Total and Fractionated Bilirubin during the First Week in the Neonatal Intensive Care Unit

Ahmed Asfari, M.D., Carolyn R. Ahlers-Schmidt, Ph.D., Barry T. Bloom, M.D.
University of Kansas School of Medicine-Wichita
Department of Pediatrics, Wichita, KS

Abstract

Background. Fractionated bilirubin requires more blood (0.6 ml) than total bilirubin alone (0.2 ml). Our focus during the first week in the Neonatal Intensive Care Unit (NICU) is on prevention of Bilirubin Induced Neurologic Dysfunction and kernicterus, which do not require fractionation. We wanted to determine the benefit of knowing fractionated bilirubin in the first week.

Methods. In this retrospective study, data were obtained from the first week for 1202 NICU inborn admissions.

Results. Direct bilirubin was more than 2.0 mg/dl in only six infants (0.6%). Five had multisystem injury from hypoxic ischemic events. One also had congenital cytomegalovirus and another had a postoperative liver hematoma. Weekly multichem profiles would have detected these abnormalities. No specific therapy was initiated for any of these infants.

Conclusions. Converting to total bilirubin alone would not alter treatment, but could reduce iatrogenic blood loss by 2.4 ml per infant.

KS J Med 2014; 7(4):129-131.

Introduction

Jaundice exists when a newborn has a high level of bilirubin in the blood.[1] Bilirubin is produced from hemoglobin when red blood cells breakdown. While in utero, the placenta allows fetal unconjugated bilirubin to transfer to the mother for conjugation and excretion. After birth, the newborn adapts and the liver begins to conjugate bilirubin so it can be excreted in the stool. The increase in conjugation takes about three days for full-term infants and longer for premature infants. The unconjugated bilirubin rises and causes jaundice. Most jaundice is not harmful; however, bilirubin may be a concern for infants with other illnesses, including prematurity. The complications of elevated bilirubin are Bilirubin Induced Neurologic Dysfunction (BIND) and a more devastating permanent syndrome, kernicterus.[2]

The diazo reaction, the routine clinical testing method for serum bilirubin, identifies direct bilirubin, the component that reacts rapidly to the diazo reagent.[3] With an accelerator, the diazo reaction measures total bilirubin (TB); this additional component we call the indirect fraction. Although highly variable, total bilirubin is the clinical surrogate used to predict the risk of BIND and kernicterus. Clinicians use frequent determinations (daily or more often) of TB to guide therapy.[4] Therapeutic interventions include phototherapy and exchange transfusion to reduce TB and the attendant risks of BIND and kernicterus.

Direct Bilirubin (DB) results monitor the excretion process, which may be impaired, by infection or long term parenteral nutrition. Both disease states typically present later in the neonatal course.[5] TB can be done on a blood sample of 0.2 ml used for blood gas and electrolyte determination. Fractionated bilirubin requires 0.6 ml. Daily or more frequent determinations of bilirubin are obtained in the first week to prevent BIND and kernicterus. Later in the course,

weekly monitoring of alkaline phosphatase, renal function, fractionated bilirubin and liver enzymes is obtained for those on long term parenteral alimentation.

Our initial objective was to determine the number and results of the bilirubin determinations during the first seven days for our Neonatal Intensive Care Unit (NICU) admissions. The second objective was to determine if any clinical insight was gained by having the direct bilirubin results during this period of time. If these infants could be managed without fractionating the bilirubin in the first week, the reduction in iatrogenic blood loss may prevent anemia and reduce transfusions.

Methods

The NICU at Wesley Medical Center has a data warehouse for information from the admission, transfer, discharge summaries, and daily progress notes, including laboratory results. These codified and text fields are stored in a series of tables in Microsoft SQL.

In this retrospective descriptive study, data were obtained from the first seven days of a convenience sample of 1202 inborn NICU admissions (7290 bilirubin levels) from January 1, 2010 to December 31, 2011. A threshold for DB of more than 2 mg/dl was set as clinically significant. Any specific intervention or diagnostic testing that was pursued in the first week related to any of the elevated direct bilirubin levels was recorded. Infants with documented inborn errors of metabolism, positive initial blood culture, or major congenital anomaly were excluded.

The research dataset was de-identified to protect patient privacy. The project was approved by the Institutional Review Board.

Results

After reviewing 1201 infants (see Table 1), only six infants (0.6%) were identified with DB more than 2 mg/dl in the first week. Of the six infants, five had multisystem injury from hypoxic ischemic events near birth. One of these also had congenital cytomegalovirus and one had surgery for a persistent vitelline duct with a liver hematoma.

Table 1. Birth weight and gestational age of infants.

	Birth Weight	Gestational Age
Mean	33	2168
SD	4	857
Median	34	2105
25th Percentile	31	1569
75th Percentile	36	2671

Discussion

Given that none of the conditions associated with elevated DB require targeted intervention during this time frame, conversion to TB alone in the first seven days of the patients in the NICU would reduce iatrogenic blood loss by an average of 2.4 ml/infant and would not alter treatment plans. The weekly fractioned bilirubin was adequate for the management and prevention of conditions associated with conjugated hyperbilirubinemia.

Acknowledgments

The Wichita Medical Research and Education Foundation funded this project. We appreciated the contributions of Jared Shaw, Paula Delmore, Joy Nimeskern, and the staff of the NICU and administration at Wesley Medical Center.

References

[1] American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of

gestation. Pediatrics 2004; 114(1):297-316. PMID: 15231951.

[2] Oh W, Tyson JE, Fanaroff AA, et al. Association between peak serum bilirubin and neurodevelopmental outcomes in extremely low birth weight infants. Pediatrics 2003; 112(4):773-779. PMID: 14523165.

[3] van de Bor M, Ens-Dokkum M, Schreuder AM, Veen S, Brand R, Verloove-Vanhorick SP. Hyperbilirubinemia in low birth weight infants and outcome at 5 years of age. Pediatrics 1992; 89(3):359-364. PMID: 1371340.

[4] Wennberg RP, Ahlfors CE, Bhutani VK, Johnson LH, Shapiro SM. Toward understanding kernicterus: A challenge to improve the management of jaundiced newborns. Pediatrics 2006; 117(2):474-485. PMID: 16452368.

[5] Yeo KL, Perlman M, Hao Y, Mullaney P. Outcomes of extremely premature infants related to their peak serum bilirubin concentrations and exposure to phototherapy. Pediatrics 1998; 102(6):1426-1431. PMID: 9832580.

*Keywords***:** hyperbilirubinemia, direct bilirubin, hemolytic anemia, neurologic dysfunction, kernicterus

Identifying Awareness, Use, and Perceptions of text4baby among Family Medicine and Obstetrics and Gynecology Practitioners at the University of Kansas Medical Center

Brent Bjornsen, MS4[1], Mark McHaney, MS4[1], Katie Merando, MS4[1], Cameron Tusken, MS4[1], Christie Befort, Ph.D.[2], Cristi Cain, M.P.H.[3], Pam Shaw, M.D.[4]
[1]University of Kansas School of Medicine, Kansas City, KS
[2]University of Kansas School of Medicine, Kansas City, KS
Department of Preventive Medicine and Public Health
[3]Kansas Department of Health and Environment, Topeka, KS
[4]University of Kansas School of Medicine, Kansas City, KS, Department of Pediatrics

Abstract

Background. Low income minority women who receive inadequate or no prenatal care have greater infant morbidity and mortality in the postnatal period. Mobile health or mHealth initiatives such as text4baby are presumed to be a means to reach underserved pregnant and postpartum women to increase their use of prenatal and postnatal care. Providers are an important referral source for mHealth initiatives. It is important, therefore, to assess the awareness, use, and perceptions of the text4baby program among Family Medicine and Obstetrics/Gynecology (Ob/Gyn) providers to determine the means to increase referrals and improve outcomes for pregnant mothers and infants.

Methods. Family medicine and Ob/Gyn providers (attending physicians, residents, nurse practitioners, nurses, and medical assistants) at the University of Kansas Medical Center (KUMC) completed a survey assessing awareness of use and perceived utility of text4baby as well as experience with technology and reservations about mHealth in general.

Results. Seventy-eight providers (38 in Family Medicine and 40 in Ob/Gyn) responded to the survey. Awareness of text4baby among all providers was 18%. Among the 14 providers who knew about text4baby, one individual stated he/she regularly refers patients to text4baby and 11 agreed that text4baby is a useful tool for the care of pregnant patients. Comparison of text4baby awareness by demographic factors showed no significant differences between any of the groups. Providers who knew of mHealth applications were more likely to know about text4baby ($p = 0.04$). Older providers were less likely to have reservations about using mHealth in their practice ($p = 0.02$). There was widespread agreement (87%) that providing evidence to clinicians that text4baby improves outcomes would increase use of the service in clinical practice.

Conclusions. Awareness of text4baby among practitioners at KUMC is minimal; use is negligible. Our study identified lack of awareness of the text4baby service and of supporting evidence about its effectiveness as the primary barriers to referral.

KS J Med 2014; 7(4):132-138.

Introduction

Low income minority women who receive inadequate or no prenatal care have greater infant morbidity and mortality in the postnatal period.[1] These women often do not receive prenatal screening or education about their pregnancy, which would improve the health outcomes of newborns.[2-5] These women also have lower levels of attendance at maternal postnatal visits, well-child visits, immunization completions, and acute care visits.[1] One potential way to improve uptake of prenatal care and the health outcomes of these women is through the use of a mobile health (mHealth) system such as text4baby.

mHealth initiatives such as text4baby are an important means by which to reach underserved pregnant and postpartum women, as long as the enrollment process is as simple as possible.[6] text4baby (https://www.text4baby.org) sends up to 267 messages to pregnant women and mothers of newborns, containing a breadth of information including prenatal health habits, signs and symptoms of labor, when to seek the expert counsel of a physician, and appointment reminders. This is done based on the mother-to-be's due date to provide information appropriate for her gestational milestones.

The potential impact of text4baby is due in part because 90% of women in the US have cell phones and texting is more prevalent among women of childbearing age and minority groups.[7] Additionally, as much as 96% of pregnant women are interested in receiving text messages regarding prenatal care.[8] Educating these pregnant women through text4baby may increase prenatal care utilization, thus pregnancy outcomes and postnatal care utilization.[1] In preliminary studies, text4baby and similar text message services have improved the health of mothers. Mothers receiving text4baby have better glucose control and report being more satisfied with their prenatal care, having higher confidence, and being less anxious about their pregnancy compared to mothers in a control group.[9,10]

Current evidence supports the use of text messaging as a tool for behavior change.[11] However, the first step in the success of text4baby is increasing its utilization by patients. Advertisements to encourage enrollment in the program range from billboards to magazine spreads. Physicians are an important expert opinion for patients, especially regarding new mobile services such as text4baby. There is, potentially, a lack of knowledge among health care providers regarding the text4baby program which may reduce its reach and effectiveness. In 2013, the Kansas Department of Health and Environment awarded mini-grants to 32 programs serving 54 total counties to increase awareness of the service among pregnant women. However, while there was one program targeting Kansas City, KS, it utilized the funds in conjunction with movie theaters in the far western area of the county for direct marketing to pregnant women.[12] This represented only a minority of the population of Wyandotte County and did not target awareness among medical providers.

U.S. News and World Report named the University of Kansas Hospital as the leading center for women's health in the region, and there are over 40,000 visits to the Ob/Gyn clinics each year.[13] Patient visits to Family Medicine clinics at the University of Kansas Hospital totaled 28,477 in 2013. There exists a vast opportunity for mHealth to provide an efficient means by which to affect patient care. Because providers can play a key role in mHealth effectiveness by referring to and reinforcing the intervention messages, it is important to assess their awareness, use, and perceptions of the service. This study surveyed the University of Kansas Family Medicine and Ob/Gyn practitioners to assess current awareness and determine any means by which to improve text4baby utilization.

Methods

Participants and setting. Survey respondents were members of the KUMC Family Medicine and Ob/Gyn departments, including faculty, residents, nurse practitioners, physician assistants, nurses, and medical assistants. A REDCap™ survey was created and distributed via email to identified providers, as well as in person at the Family Medicine clinic and resident conferences for both specialties.

Measures. Survey domains assessed knowledge of the text4baby program

(awareness), referral of text4baby program to patients (use), and perceived usefulness of and barriers to the text4baby program (including patient compliance, health and technological literacy, and privacy issues). Additional variables included field of practice, practitioner role, age, gender, frequency of seeing pregnant patients, personal and professional text message use, awareness and use of mHealth, patients asking about mHealth, reservations about mHealth, and willingness to adopt text4baby if provided evidence it improved outcomes.

Sample size justification. A total of 135 individuals were identified as providers in the Family Medicine and Ob/Gyn departments. A sample size of 43 would provide a 95% confidence interval of ± 10% around our estimated current awareness of 20%.

Statistical analysis. Univariate statistics were used to describe variables. Chi-square analyses were used to examine correlates of awareness, use, and perception of text4baby among practitioners.

Results

One-hundred thirty-five surveys were distributed and a total of 78 providers responded (58% response rate, 38 Family Medicine and 40 Ob/Gyn providers). Respondent characteristics, mobile use, and mHealth reservations are described in Table 1. Among questions identifying mobile use, 92% (n = 72) of respondents reported texting for personal use compared to 50% (n = 39) who text for professional use and 47% (n = 37) who use mobile devices to access patient health information. Only 8% (n = 6) indicated that patients regularly ask them about mHealth applications.

Eighteen percent (n = 14) of respondents were aware of the text4baby program (see Table 2). Among these providers who were aware, one individual stated he/she regularly refers patients to text4baby (1.6% of the total sample), 11 (79%) agreed that they believe text4baby is a useful tool for the care of pregnant patients, and 10 (72%) indicated if they were to refer, socioeconomic status, age, and insurance status of the patient would not play a role in their decision to refer (90%, 80%, and 100% respectively

Table 1. Provider characteristics (n = 78).

Characteristic	n	%
Field Of Practice		
Family Medicine	38	48.7%
Ob/Gyn	40	51.3%
Practitioner Role		
Attending Physician	30	38.5%
Resident	24	30.8%
Nurse Practitioner	3	3.9%
Registered Nurse	20	25.6%
Medical Assistant	1	1.3%
Age		
18-35	41	52.6%
36-55	28	35.9%
> 55	9	11.5%
Gender		
Male	15	19.2%
Female	63	80.8%
Regularly see pregnant patients in practice	59	75.6%
Mobile Knowledge/Habits		
Regularly text for personal use	72	92.3%
Regularly text for professional use	39	50.0%
Aware of mHealth applications for patient care	42	53.9%
Regularly asked by patients about mHealth applications	6	7.7%
Regularly use mobile device to access patient health information	37	47.4%

said that these issues do not play a factor).

Thirty-nine percent (n = 30) of providers stated they have no reservations to using mobile health applications in their regular practice (see Table 2). Of the remaining 61% (n = 48), a variety of barriers were endorsed including patient health literacy, program efficacy, compliance concerns, and patient privacy. Eighty-seven percent (n = 68) of respondents agreed that if evidence was provided regarding text4baby efficacy for improving health outcomes for pregnant patients and their infants, they would be likely to incorporate the program into their regular practice.

Table 2. Awareness and use of text4baby and reservations to mHealth (n = 78).

Variable	**n**	**%**
Aware of text4baby	14	18.0%
Regularly refer patients to text4baby	1	-
Believe text4baby is a useful tool	11	-
Likely to refer to text4baby provided evidence supporting improved outcomes	68	87.2%
Reservations about mHealth		
Patient Privacy	9	11.5%
Patient Compliance	11	14.1%
Time Concerns	8	10.2%
Patients Do Not Have Resources to Make Change	6	7.7%
Patient Tech Literacy	9	11.5%
Patient Health Literacy	18	23.1%
Program Efficacy Concerns	12	15.4%
Patient Education Material Availability	7	9.0%
No Reservations	30	38.5%

Comparison of the awareness of text4baby by demographic factors (specialty, role in patient care, age, and sex) showed no significant difference between any of the groups. Providers who *were aware* of other mHealth applications also were more likely to be aware of text4baby ($p = 0.04$). Physicians were more likely to be willing to refer to text4baby than non-physician providers ($p = 0.03$). Providers age 18-34 and 35-54 were more likely to have reservations about using mHealth applications compared to providers over the age of 55 ($p = 0.02$). Providers who regularly see pregnant patients also had more reservations about using mHealth compared to providers who do not routinely see pregnant patients ($p = 0.05$).

Discussion

Text4baby is a growing mHealth initiative that shows promise in practitioners' ability to provide supplemental important health information to pregnant patients outside of the practice setting. To date, over 650,000 individuals

have signed up for the program, a number which continues to rise.[14] However, many women who would benefit from this program may not be aware of its existence, due to both a lack of provider awareness and marketing issues.

The World Health Organization reported that there is a lack of knowledge concerning the possible applications of mHealth, both among providers and non-providers; this exemplifies the ongoing need to keep providers informed of trends and developments in the field, and communicate mHealth research findings and evaluations within the broader context of patient care.[15]

This knowledge gap is being addressed on a larger scale in various projects and studies across the world; however, there is room for a hyper-local lens to examine the use and efficacy of mHealth in Kansas. Our goal was to assess the awareness, use, and perceptions of the text4baby program among Family Medicine and Ob/Gyn providers.

Awareness of text4baby was minimal at KUMC, and only one provider said he/she regularly refers patients to the program. Providers' field of practice, age, gender, or role did not correlate with awareness of the program. There also was no difference in awareness of text4baby between providers who *used* other mHealth applications in their practice and those who did not. This may, perhaps, point to a lack of direct marketing to providers about the text4baby service rather than an unwillingness of providers to use the service per se.

Providers' mobile device use was much higher for personal than for professional use, with only half of them regularly texting and using mobile devices for professional use. Surprisingly, providers over the age of 55 were less likely to have reservations regarding the use of mHealth applications. The reason for this is unclear. Perhaps younger generations have a more inherent conscience of the barriers and failures of technology. Additionally, providers who regularly see pregnant patients in their practice were more likely to have reservations about using mHealth compared to those who never/rarely do. Further study is needed to explore the reasons behind provider perceptions regarding mHealth applications. Regardless, many of the reservations and barriers that we identified are echoed in larger studies about mHealth. The World Health Organization commented in its second annual survey about eHealth:

> Many of the top six barriers to mHealth implementation are related to the need for further knowledge and information, such as assessing effectiveness and cost-effectiveness of mHealth applications. Other key barriers included conflicting health system priorities, the lack of supporting policy, and legal issues. [15]

Additional study, especially in Kansas, should be directed at identifying beliefs behind these barriers and methods of minimizing their impact upon the using of mHealth.

Very few providers indicated that they are regularly asked by patients about mHealth services. Providers likely would not know if their patients are using such programs as patients often do not report where they receive other health information. With providers being unaware of common mHealth services being marketed to patients, there is a potential lost opportunity for them to address important patient health information needs. Perhaps, the most important finding of this study was that the majority of providers likely would utilize text4baby if evidence was provided to them that it improved outcomes. Seminars, webinars, or other methods could provide avenues by which providers can learn about tools like text4baby and their usefulness in their regular practice.

Conclusion

Awareness of text4baby among practitioners at KUMC is minimal and its use is negligible. Our study identified this issue and attempted to elicit the perceptions that play into this reality. It remains a program which has a strong potential to provide quality care to pregnant patients and improve outcomes. With this in mind, further studies and initiatives are needed to identify reasons for incorporating such a program into practice and perceptions of mHealth in general. Furthermore, additional studies are needed to examine the efficacy of the program and to improve its uptake by the targeted low socioeconomic pregnant population.

References

[1] York R, Tulman L, Brown K. Postnatal care in low-income urban African American women: Relationship to level of prenatal care sought. J Perinatol 2000; 20(1):34-40. PMID: 10693098.

[2] Crowther CA, Hiller JE, Moss JR, et al. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med 2005; 352(24):2477-2486. PMID: 1595174.

[3] Gilson GJ, Christensen F, Romero H, Bekes K, Silva L, Qualls CR. Prevention of group B streptococcus early-onset neonatal sepsis: Comparison of the Center for Disease Control and Prevention screening-based protocol to a risk-based protocol in infants at greater than 37 weeks' gestation. J Perinatol 2000; 20(8 Pt 1):491-495. PMID: 11190588.

[4] Wilson RD, Davies G, Désilets V, et al. The use of folic acid for the prevention of neural tube defects and other congenital anomalies. J Obstet Gynaecol Can 2003; 25(11):959-973. PMID: 14608448.

[5] Chung M, Raman G, Trikalinos T, Lau J, Ip S. Interventions in primary care to promote breastfeeding: An evidence review for the U.S. Preventive Services Task Force. Ann Intern Med 2008; 149(8):565-582. PMID: 18936504.

[6] Gazmararian JA, Elon L, Yang B, Graham M, Parker R. Text4baby program: An opportunity to reach underserved pregnant and postpartum women? Matern Child Health J 2014; 18(1):223-332. PMID: 23494485.

[7] Jordan ET, Ray EM, Johnson P, Evans WD. Text4Baby: Using text messaging to improve maternal and newborn health. Nurs Womens Health 2011; 15(3):206-212. PMID: 21672170.

[8] Cormick G, Kim NA, Rodgers A, et al. Interest of pregnant women in the use of SMS (short message service) text messages for the improvement of perinatal and postnatal care. Reprod Health 2012; 9:9. PMID: 22866753.

[9] Grabosch S, Gavard JA, Mostello D. Text4baby improves glycemic control in pregnant women with diabetes. [Abstract]. Am J Obstet Gynecol 2014; 210(1):S88.

[10] Jareethum R, Titapant V, Chantra T, Sommai V, Chuenwattana P, Jirawan C. Satisfaction of healthy pregnant women receiving short message service via mobile phone for prenatal support: A randomized controlled trial. J Med Assoc Thai 2008; 91(4):458-463. PMID: 18556852.

[11] Cole-Lewis H, Kershaw T. Text messaging as a tool for behavior change in disease prevention and management. Epidemiol Rev 2010; 32(1):56-69. PMID: 20354039.

[12] text4baby.org. Text4baby - State Partner Spotlights. Text4baby - Minigrants Signif-icantly Increased Enrollment in Kansas! Available at: https:// text4baby.org/index.php/get-involved-pg/partners/stateorganizations/2-uncategorised/97. January 14, 2014. Accessed February 4, 2014.

[13]University of Kansas Medical Center. Shining Through: Department of Obstetrics and Gynecology 2012 Annual Report. Available at: http://www.kumc.edu/Documents/obgyn/AR2012. Accessed March 5, 2014.

[14]text4baby.org. text4baby Enrollment Data. Available at: https://text4baby.org/index.php/get-involved-pg/partners/national-organization/7-partner-resources/105. Accessed March 5, 2014.

[15]World Health Organization. MHealth: New Horizons for Health through Mobile Technologies. World Health Organization; 2011. Available at: http://www.who.int/goe/publications/goe_mhealth_web.pdf. Accessed May 23, 2014.

Keywords: mobile applications, text messaging, prenatal care, pregnancy

Prevalence and Predictors of Social Support Utilization among Cancer Patients Undergoing Treatment

John Hunninghake, M.D.[1], Fanglong Dong, Ph.D.[2], Robert B. Hines, Ph.D.[2], Elizabeth Ablah, Ph.D.[2], Sarah Taylor, M.D.[3]
[1]San Antonio Military Medical Center, San Antonio, TX
[2]University of Kansas School of Medicine-Wichita
Department of Preventive Medicine and Public Health
[3]University of Kansas School of Medicine-Kansas City
Department of Internal Medicine, Division of Hematology and Oncology

Abstract

Background. The purpose of this study was to quantify the prevalence of cancer patients utilizing social support services while undergoing treatment and to identify patient and clinical factors associated with utilization of such services.

Methods. This was a cross-sectional study. Surveys were distributed to three cancer clinics at 11 locations in the greater Kansas City metropolitan area in 2010. Study inclusion criteria included being at least 18 years old and undergoing treatment for cancer at the time of survey completion.

Results. A total of 465 oncology patients completed surveys. Two-thirds (67.5%, n = 314) were undergoing treatment for cancer and were included in the final analysis. More than half (63.7%, n = 198) were female, and the average age was 58.9 ± 13.3 years. More than one-third (37.4%, n = 117) reported using cancer-related social support services. Additionally, 22% (n = 69) reported not using support services but were interested in learning more about those services. Patients had increased odds of having used support services if they were female (OR = 2.67; 95% CI = 1.47, 4.82), were younger adults, or had stage I-III (OR = 2.67; 95% CI 1.32, 5.26) or stage IV cancer (OR = 2.3; 95% CI 1.14, 4.75) compared to those who did not know their cancer stage.

Conclusions. More than one-third of patients reported using social support services. A substantial portion of participants reported not using support services but were interested in learning more about those services. Increasing social support service utilization might be especially important to explore for men, those who do not know their cancer stage, and older adults.

KS J Med 2014; 7(4):139-148.

Introduction

In the United States, approximately 1.6 million new cancers are diagnosed annually, and cancer remains the second most-common cause of death after heart disease.[1] Cancer and its treatment can lead to physical disability, psychological distress, and increased healthcare needs.[2] People diagnosed with cancer experience many physical, family, emotional, practical, and spiritual needs during the acute treatment and chronic management of their cancer.[3] Services and programs have been developed to address these needs. Patients consider these services as part of high quality cancer care and expect cancer therapy providers to address their supportive care needs.[4]

Social support services are an important factor contributing to decreased distress and improved psychosocial adjustment among cancer patients at all stages of the disease trajectory.[5] Social support services can be defined as services or programs that help a person with cancer and their families cope with cancer, from pre-diagnosis through

treatment and cure, or death and bereavement.[6] Bey proposed to incorporate supportive care as part of the continuous care for cancer patients.[7] These services can be provided through social workers or nonprofit agencies.

The prevalence of utilizing supportive services varied greatly from one study to another.[4] One study estimated that 8.2% of active cancer patients utilized one or more support services offered by a social worker during the previous 12 months.[8] Another study reported that 15% to 25% of cancer patients used cancer-related social support services throughout the trajectory of their disease.[9] Due to the great variability of supportive services utilization and diversity of methods used in different studies, limited research has explored factors associated with under-utilization of such social support services.[4] Two studies suggested that younger cancer patients (compared to older) may be more inclined to utilize social support services.[8,10] However, it is unclear whether other factors (e.g., cancer stage) may be associated with utilization of cancer-support services. Identifying these factors may help clinicians and social workers target vulnerable populations who could benefit from cancer-related social supportive services.

The purpose of this study was to determine the prevalence of social support service usage among adult cancer patients who were undergoing cancer therapy. Additionally, this study sought to identify significant factors associated with support services utilization.

Methods

Participants. This was a cross-sectional study of cancer patients who attended one of three different oncology outpatient clinics at 11 locations in the Kansas City metropolitan area in 2010. The three clinics included Kansas City Cancer Center with seven locations, the University of Kansas Cancer Center with three locations, and the University of Kansas Radiation Oncology Clinic with one location. The inclusion criteria were: being at least 18 years old, undergoing treatment for cancer (chemo-therapy, radiation therapy, or both) at the time of survey completion, able to speak English, and able to give informed consent.

Instrument. The primary method of data collection was a two-page survey with 13 multiple-choice questions. Survey questions included patients' demographic information (age, gender), cancer stage (stage I-III, stage IV, and unknown stage), and whether they were undergoing treatment for cancer currently and if so, the type of treatment (chemotherapy, radiation, or both). The survey included an item regarding whether the respondent was using one or more social support services. If patients were not using a service, they were asked to discontinue the survey. For respondents who were utilizing one or more support services, additional multiple-choice questions with open-ended, write-in options included: the specific services utilized (e.g., counseling, support groups, transportation, wellness programs, financial assistance), specific nonprofit agencies that provide the services, service used most often, reasons for using support services (e.g., personal preference, avail-ability, saves money), source of information about the service (e.g., doctor, nurse, social worker), whether the service improved coping ability, the importance of services (rated on 1-10 scale), type of support provided (e.g., emotional, spiritual, physical), whether the respondent discussed support services with the doctor and/or nurse, and their opinions of whether every cancer clinic should offer information about services to patients.

The primary outcome measure in this study was utilization of one or more social support services. There were four possible

responses to the primary outcome: (1) "Yes, I use one or more social support services," (2) "No, I do not use support services but I WOULD be interested in learning more about them," (3) "No, I do not use support services, and I would NOT be interested in learning more about them," and (4) "Unsure". Response options (2), (3), and (4) were categorized as "does not use a support service," and (1) was coded as "uses at least one support service." Additionally, if the respondent checked any of the 19 listed support services or responded to an open-ended question regarding their use of the support services, the respondent was coded as "uses at least one support service".

Variables associated with support service utilization included gender (male vs female), age (continuous variable), cancer stage (stage I-III, stage IV, and did not know cancer stage)[11], time since original diagnosis (< 3 months, 3 months to 1 year, and ≥ 1 year), type of treatment received (chemotherapy, radiation, or both), and location of treatment. The location of treatment was used to determine if difference in service utilization occurred by site, but it also served as a proxy for the presence of a full-time social worker. Two clinic locations employed full-time social workers, whereas the third relied on nurses to provide information.

Procedures. Surveys were distributed to three different cancer clinics, both academic and non-academic, at 11 locations in the greater Kansas City metropolitan area. Surveys were completed voluntarily. The specific distribution method at each clinic varied according to the policies of the respective clinical location. Generally, surveys were placed on waiting room tables, completed by patients while waiting in the exam room, or solicited for completion by a single investigator who spent about six days in the waiting rooms at high-volume cancer clinics. Completion of the survey was considered informed consent for the study. This study was approved by the Human Subjects Committee at the University of Kansas Medical Center and the Institutional Review Boards at each clinic.

Statistical analysis. All analyses were conducted using SAS software for Windows (version 9.3, Cary, North Carolina). Descriptive statistics were presented as frequencies and proportions for categorical variables, and means and standard deviations were presented for continuous variables. A Chi-square analysis was conducted to identify the association of demographic variables with the reported support-service utilization. Analysis of variance (ANOVA) was conducted to identify whether there was age differences among three different support service utilization groups. Logistic regression analysis was conducted to identify factors associated with support service utilization (dichotomous variable, utilized one or more support services vs did not utilize support service). The possible predictors included: gender, age, and cancer stage, time since the original diagnosis, type of treatment, and location of receiving treatment. Odds ratios (ORs) with 95% confidence intervals (CIs) were reported. To obtain a meaningful interpretation of the odds ratio for age, 5-year increments were used.

The initial selection of potentially significant predictors was conducted using simple logistic regression with the sole factor included in the model. The significance level was set as 0.10. With the potentially significant predictors identified, a multiple logistic regression analysis was conducted to identify the final significant predictors. The interaction terms were included in the initial logistic regression model. If the interaction terms were not significant, they were removed from the logistic regression model and only the main effect was included in the final model. The

Hosmer-Lemeshow goodness-of-fit test assessed how well the logistic regression model fit the data. The significance level for the multiple logistic regression analysis was set as 0.05. All tests were two-sided.

Results

Among the 465 respondents who completed the survey, 314 were undergoing cancer treatment and included in the final analysis. Table 1 presents demographic information about these participants. The average age of respondents was 58.9 ± 13.3 years. Almost two-thirds (63.7%, n = 198) of the respondents were female, 58.2% reported being 41 to 65 years, and 68.4% reported having stage I-III or IV cancer (n = 210). Additionally, 44.5% (n = 138) of respondents reported having cancer for more than one year since the original diagnosis, and most patients (72.2%) were undergoing chemotherapy. A slim majority of patients (51.8%) were treated at Kansas City Cancer Center. More than one-third of respondents (37.4%, n = 117) reported using one or more social support services while undergoing treatment for cancer, yet a slightly larger proportion (40.3%, n = 126) reported not using a support service and reported they were not interested in learning more about the services.

Chi-square analysis was conducted to determine the association between support service utilization status and potential associated factors. Since only one participant reported "unsure" about social support utilization, that category was excluded from the Chi-square analysis. Table 2 presents the results of the Chi-square analysis. A significantly larger proportion of women than men reported using one or more support services (46.2% vs 22.3%, $p < 0.01$). Younger age was associated with a higher proportion of utilizing one or more support service (71.7% among those aged 18 to 40 years; 40.2% among those aged 41 to 65 years; 26.1% among those aged 66 to 80 years; and 7.1% among those aged 81 years or older, $p < 0.01$). Compared to patients who did not know their cancer stage (18.9%), 48.3% of stage I-III and 41.3% of stage IV patients reported using one or more social support service ($p < 0.01$). There was no difference in the utilization of social support services based on patients' duration since their original diagnosis ($p = 0.96$), the type of treatment utilized ($p = 0.64$), or location of the clinic ($p = 0.79$).

The results of the logistic regression analysis are presented in Table 3. The three factors identified in the Chi-square analysis, gender, age, and cancer stage, remained significantly associated with support service utilization. No interaction term was significant ($p = 0.34$ for age and gender interaction, $p = 0.38$ for age and cancer stage interaction, $p = 0.80$ for gender and cancer stage interaction). Women had increased odds (OR = 2.67; 95% CI 1.47, 4.82, $p < 0.01$) of utilizing support services compared to men. For every five-year increase in age, there was a 13% decreased odds of support service utilization ($p < 0.01$). Finally, compared to respondents who did not know their cancer disease stage, those with stage I-III (OR = 2.67; 95% CI 1.32, 5.26) or stage IV (OR = 2.30; 95% CI 1.14, 4.75) had increased odds of utilizing support services ($p = 0.03$ for the overall cancer stage effect). The Hosmer-Lemeshow goodness-of-fit test yielded a value of 11.51 ($p = 0.17$), which indicated a good fit of the logistic model for the data.

Discussion

In this study, more than one-third (37.4%) of cancer patients reported using one or more social service. Women were more likely to utilize social support services compared to men. Younger patients were more likely to utilize support services while

Table 1. Respondents' demographics (N = 314).

Gender	**Frequency**	**Percent**
Male	113	36.3%
Female	198	63.7%
Age		
18-40 Years	28	9.0%
41-65 Years	181	58.2%
66-80 Years	88	28.3%
> 81 Years	14	4.5%
Stage of Cancer		
Stages I-III	118	38.4%
Stages IV	92	29.7%
Did not know	97	31.6%
Time Since Original Diagnosis		
Less than 3 months	47	15.2%
3 months to 1 year	125	40.3%
More than 1 year	138	44.5%
Type of Treatment		
Chemotherapy	215	72.2%
Radiation	34	11.4%
Chemotherapy and Radiation	49	16.4%
Location		
Kansas City Cancer Center	162	51.8%
University of Kansas Cancer Center	101	32.3%
University of Kansas Radiation Oncology Clinic	50	16.0%
Social Support Service		
Used one or more social support service	117	37.4%
Did not use a support service, and was not interested in learning more	126	40.3%
Did not use a support service, but was interested in learning more	69	22.0%
Unsure	1	0.3%

Table 2. Comparison of support service utilization among potential predictors.

	Did not use a support service, and was not interested in learning more	Did not use a support service, but was interested in learning more	Used one or more social support service	p-value
Gender (n; %)				< 0.01
Male	59 (52.7%)	28 (25%)	25 (22.3%)	
Female	66 (33.5%)	40 (20.3%)	91 (46.2%)	
Age				< 0.01
18-40 Years	5 (17.9%)	3 (10.7%)	20 (71.4%)	
41-65 Years	64 (35.8%)	43 (24%)	72 (40.2%)	
66-80 Years	50 (56.8%)	15 (17%)	23 (26.1%)	
≥ 81 Years	6 (42.9%)	7 (50%)	1 (7.1%)	
Age in Years (Mean ± SD)	54.4 ± 13	59.7 ± 14	62.5 ± 12.3	< 0.01
Cancer Stage (n; %)				< 0.01
Stages I-III	37 (31.4%)	24 (20.3%)	57 (48.3%)	
Stage IV	33 (35.9%)	21 (22.8%)	38 (41.3%)	
Did not know stage	54 (56.8%)	23 (24.2%)	18 (18.9%)	
Time Since Original Diagnosis (n;%)				0.96
Less than 3 months	20 (42.6%)	11 (23.4%)	16 (34%)	
3 months to 1 year	47 (38.2%)	28 (22.8%)	48 (39%)	
More than 1 year	58 (42%)	29 (21%)	51 (37%)	
Type of Treatment (n; %)				0.64
Chemotherapy	87 (40.7%)	46 (21.5%)	81 (37.9%)	
Chemotherapy and radiation	16 (33.3%)	9 (18.8%)	23 (47.9%)	
Radiation	14 (41.2%)	9 (26.5%)	11 (32.4%)	
Location (n; %)				0.79
Kansas City Cancer Center	70 (43.5%)	32 (19.9%)	59 (36.6%)	
University of Kansas Cancer Center	38 (37.6%)	24 (23.8%)	39 (38.6%)	
University of Kansas Radiation Oncology Clinic	18 (36.7%)	13 (26.5%)	18 (36.7%)	

Table 3. Odds Ratio Estimates with 95% Confidence Interval for Service Utilization

Effect	**Unadjusted OR**	**Adjusted OR**
Gender		
Male	Reference	Reference
Female	2.98 (95% CI 1.77, 5.05)	2.67 (95% CI 1.49, 4.91)
Age (based on 5-year increments)	0.81 (95% CI 0.74, 0.89)	0.87 (95% CI 0.78, 0.96)
Cancer Stage		
Did not know stage	Reference	Reference
Stage I-III	4.00 (95% CI 2.13, 7.49)	2.67 (95% CI 1.32, 5.26)
Stage IV	3.01 (95% CI 1.56, 5.82)	2.30 (95% CI 1.14, 4.75)

undergoing cancer treatment than older patients. Those who knew their cancer stage were more likely to utilize the social support service compared to those who did not know their cancer stage. Duration since the patient's original diagnosis, treatment type, and treatment site were not associated with utilization of cancer-related support services.

The reported 37.4% prevalence of social support utilization was higher than what has been reported in the literature (15-25%).[9] This difference may be attributable to multiple factors, including different definitions of social support services,[6,7] differences in the types of social support services (e.g., psychological, physical, spiritual) that were eligible to be included in the study,[4] and availability of social support services for cancer patients in different regions and different types of cancer.[4] Additionally, our study suggested there was a small but significant proportion (22%) of cancer patients who reported interest in learning more about available social support services, suggesting that study participants were unaware of available services. As such, cancer clinics might need to re-evaluate their method of informing patients about available services.

This study identified factors associated with social support utilization during cancer treatment including younger, female, and knowing one's cancer stage. Few studies had evaluated the prevalence of support services utilization during treatment.[2,3,12,13] Our results were similar to these studies as patients tended to have higher needs if they were younger, female, or had cancer that was not in remission.

Cancer stage was a significant factor for utilization of support services. Patients with advanced pathological cancer stages have higher patient care and support needs in the acute treatment phase than patients with less advanced cancer.[14] In this study, stage IV cancer patients had lower odds of social support services utilization compared to stage I-III cancer patients. This unexpected finding may be explained by the self-reporting mechanism of supportive service utilization. Additional research is warranted to explore why a significant subset (32%) of cancer patients did not know their cancer stage, even when given multiple choice options. More importantly, lack of knowledge regarding disease stage may be a proxy indicator of lower health literacy and/or lack of self-efficacy following a cancer diagnosis. These patients may have a higher degree of fatalism, and fail to see any benefit of social support utilization. Health-care providers should make sure all patients, but especially those with possible lower self-efficacy, are aware of cancer social support services and the specific types of support provided.

The current study found that time since cancer diagnosis was not a significant predictor for support service utilization. However, previous studies suggested that patients are more likely to utilize services during the initial time period after diagnosis due to emotional distress, psychological distress, and level of unmet needs.[2,10,14] Patients might need to be assessed regularly throughout treatment and thereafter to evaluate unmet needs that could be alleviated through support services. Research that would track the dynamic utilization of support services by cancer patients over time could elucidate nuances regarding the timing of service needs and utilization.

In contrast to similar studies, treatment type (chemotherapy, radiation, or both) was not associated with utilization. Previous research suggested that compared to no treatment, those undergoing chemotherapy are more likely to have unmet needs.[15,16] In

our study, patients who received neoadjuvant/adjuvant treatment were not compared to those who received surgery or did not undergo any form of treatment. In addition, some patients undergoing chemotherapy may report unmet needs even if they utilized social support services. Thus, our outcome may not be completely comparable with the presence of unmet needs.

Finally, there was no difference in service utilization by treatment location, suggesting that the treatment sites were similar in this regard. The presence of a full-time social worker did not increase the social support utilization by cancer patients. This lack of difference may be attributed to the various locations' relatively equal time allocation by the nurse/social worker dedicated to disseminating support service information. No previous studies had investigated the utilization of support services by social worker presence in the clinic. Future research could identify the barriers to using social support services even when the social workers are present in the clinic.

Limitations. The study data were self-reported and subject to reporting bias. The methods of survey distribution were inconsistent across clinic location and dependent upon each clinic's policies. The survey did not include self-reported demographic questions. For instance, the instrument did not include race, ethnicity, educational level, income, health insurance status, type of cancer, or current length of the treatment. Additionally, the instrument did not assess patients' treatment frequency, overall duration, or cancer type. These variables would be important to identify associations with utilization of cancer-related support services. Finally, the instrument did not collect clinical outcome data such as survival, quality of life improvement, and decreased psychological morbidity. Therefore, the results of this study should be considered hypothesis generating. Research is needed to evaluate the medical benefit of social support services and to elucidate which characteristics of patients who do not utilize social support services but may have unmet needs. Finally, the definition of "social support services" was broad. Different types and stages of cancer patients have expressed different needs.[4] Even the same type of cancer patients will express different needs.[17,18] Cawley et al.[18] listed information seeking as the unmet need for breast cancer patients, whereas Girgis et al.[17] listed information seeking, disease specific needs, and psychological and psychosocial needs. As expected, the needs for mixed types of cancer patients will vary greatly by cancer type and stage.

Conclusions

More than one-third of cancer patients reported using social support services while undergoing cancer treatment. Women and younger patients reported a higher prevalence of cancer-related support service utilization, as did those with stage I-IV cancer (compared to those who did not know their cancer stage). More than half of cancer patients utilized or were interested in learning more about social support services. Therefore, cancer clinics must be prepared to provide information about the availability and the specific types of services provided to cancer patients as an integral component of quality cancer care. Future research is needed to understand the potential unmet needs of all sub-populations, especially men, older adults, and patients who do not know their cancer stage to increase the quality of life of patients following a diagnosis of cancer.

References

[1] American Cancer Society. Cancer facts and figures. New York: American Cancer Society, 2012.

[2] Puts MT, Papoutsis A, Springall E, Tourangeau AE. A systematic review of unmet needs of newly diagnosed older cancer patients undergoing active cancer treatment. Support Care Cancer 2012; 20(7):1377-1394. PMID: 22476399.

[3] Sanson-Fisher R, Girgis A, Boyes A, Bonevski B, Burton L, Cook P. The unmet supportive care needs of patients with cancer. Supportive Care Review Group. Cancer 2000; 88(1):226-237. PMID: 10618627.

[4] Harrison JD, Young JM, Price MA, Butow PN, Solomon MJ. What are the unmet supportive care needs of people with cancer? A systematic review. Support Care Cancer 2009; 17(8):1117-1128. PMID: 19319577.

[5] Kornblith AB, Herndon JE 2nd, Zuckerman E, et al. Social support as a buffer to the psychological impact of stressful life events in women with breast cancer. Cancer 2001; 91(2):443-454. PMID: 11180093.

[6] Gysels M, Higginson IJ, Rajasekaran M, Davies E, Harding R. Improving supportive and palliative care for adults with cancer. Research Evidence Manual. London, England: National Institute of Clinical Excellence, 2004.

[7] Bey P. Future trends in oncology. Support Care Cancer 2000; 8(2):98-101. PMID: 10739355.

[8] Gadalla TM. Cancer patients' use of social work services in Canada: Prevalence, profile, and predictors of use. Health Soc Work 2007; 32(3):189-196. PMID: 17896675.

[9] Cwikel JG, Behar LC. Organizing social work services with adult cancer patients: Integrating empirical research. Soc Work Health Care 1999; 28(3):55-76. PMID: 10457981.

[10] Andersen BL. Psychological interventions for cancer patients to enhance the quality of life. J Consult Clin Psychol 1992; 60(4):552-568. PMID: 1506503.

[11] Greene FL, Page DL, Fleming ID, et al. AJCC Cancer Staging Handbook. From the AJCC Cancer Staging Manual. Sixth Edition. New York: Springer Verlag, 2002.

[12] McIllmurray MB, Thomas C, Francis B, Morris S, Soothill K, Al-Hamad A. The psychosocial needs of cancer patients: Findings from an observational study. Eur J Cancer Care (Engl) 2001; 10(4):261-269. PMID: 11806677.

[13] Matsuyama RK, Kuhn LA, Molisani A, Wilson-Genderson MC. Cancer patients' information needs the first nine months after diagnosis. Patient Educ Couns 2013; 90(1):96-102. PMID: 23058682.

[14] Chen SC, Liao CT, Lin CC, Chang JT, Lai YH. Distress and care needs in newly diagnosed oral cavity cancer patients receiving surgery. Oral Oncol 2009; 45(9):815-820. PMID: 19250858.

[15] Veloso AG, Sperling C, Holm LV, et al. Unmet needs in cancer rehabilitation during the early cancer trajectory-A nationwide patient survey. Acta Oncol 2013; 52(2):372-381. PMID: 23320774.

[16] Boyes AW, Girgis A, D'Este C, Zucca AC. Prevalence and correlates of cancer survivors' supportive care needs 6 months after diagnosis: A population-based cross-sectional study. BMC Cancer 2012; 12:150. PMID: 22510387.

[17] Girgis A, Boyes A, Sanson-Fisher RW, Burrows S. Perceived needs of women diagnosed with breast cancer: Rural versus urban location. Aust N Z J Public Health 2000;2 4(2):166-173. PMID: 10790936.

[18]Cawley M, Kostic J, Cappello C. Informational and psychosocial needs of women choosing conservative surgery/ primary radiation for early stage breast cancer. Cancer Nurs 1990; 13(2):90-94. PMID: 2331696.

Keywords: cancer, social support, psychosocial factors, cancer treatment protocol, needs assessment

Cisatracurium in Acute Respiratory Distress Syndrome

Joshua R. Howitt, Pharm.D.[1,2,3],
John D. Hill, Pharm.D. Candidate[2],
Trenton D. Nauser, M.D.[1,4]
[1]Department of Veterans Affairs, Kansas City, MO
[2]University of Missouri-Kansas City, MO
[3]University of Kansas School of Pharmacy, Lawrence, KS
[4]University of Kansas School of Medicine, Kansas City, KS

Introduction

Acute Respiratory Distress Syndrome (ARDS) is a condition characterized by damage to the alveoli and cytokine mediated inflammation, which results in the disruption of the lung endothelium and increased pulmonary edema.[1] This acute injury can result in the onset of hypoxemic respiratory failure which eventually manifests itself as multiple organ failure, pulmonary fibrosis, and pulmonary vascular destruction. Common causes include sepsis, aspiration, trauma, and pneumonia. The Berlin Definition, published in 2012, provides updated criteria for diagnosis and disease severity stratification.[2] For a diagnosis of ARDS according to this definition, the patient must experience an insulting injury or onset of hypoxemia worsening within one week, display bilateral opacities upon chest imaging, and the pulmonary edema cannot be attributed to congestive heart failure. A measure of the lung's ability to transfer inhaled oxygen to the blood stream, PaO_2/FiO_2, is used to categorize the severity of ARDS, with values of 201-300 termed mild, 101-200 moderate, and $\leq$ 100 severe. ARDS affects an estimated 190,000 patients annually in the United States, with mortality estimates ranging from 26-58%.[3-5]

Cisatracurium is an intermediate duration, non-depolarizing neuromuscular blocking agent (NMBA). It is an isomer of atracurium, which antagonizes the action of acetylcholine by competitively binding to cholinergic receptors on the motor end-plate and blocking neuromuscular transmission.[6] Cisatracurium undergoes Hofmann elimination, or non-enzymatic degradation at physiological pH and temperature, to inactive metabolites which are eliminated primarily by the liver and kidneys. Cisatracurium is indicated to relax skeletal muscles and facilitate tracheal intubation. It also can be used as an adjunct to either general anesthesia during surgery or sedation during mechanical ventilation in the intensive care unit. The two standard bolus doses of cisatracurium are 0.15 mg/kg and 0.2 mg/kg. This loading dose can be followed with a continuous infusion for maintenance, with clinical trial doses ranging from 0.5-10 mcg/kg/min, and the average maintenance dose of 3 mcg/kg/min.

Three studies, conducted by the same research team in France, have evaluated the use of cisatracurium in patients with ARDS.[7-9] The first two trials displayed an increase in oxygenation as measured by PaO_2/FiO_2 as well as a reduction in inflammatory markers IL-1, IL-6, and IL-8 associated with cisatracurium use.[7-8] These two trials indicated a trend toward decreased mortality associated with the infusion of cisatracurium. However, they did not meet

statistical significance and the studies were not powered to do so.

The third trial evaluated 90-day mortality associated with a 48-hour continuous infusion and found a non-significant trend toward reduced 90-day crude mortality, 31.6% in the cisatracurium group vs 40.7% in the placebo group ($p = 0.08$).[9] However, a statistically significant reduction was observed after adjustment for baseline PaO_2/FiO_2, plateau pressure, and the Simplified Acute Physiology II score. In a subgroup analysis, the more severe patients, characterized by a PaO_2/FiO_2 of less than 120, saw the most improvement with a statistically significant reduction in mortality.[9] A meta-analysis and systematic review conducted of these three articles concluded that compared to placebo, a 48-hour continuous cisatracurium infusion resulted in a statistically significant 28% relative risk reduction in hospital mortality.[10]

Case Report

A 60-year-old Caucasian male was brought to the emergency department via emergency medical services with a chief complaint of abdominal pain beginning three hours prior to arrival. Onset was one hour post-prandial and rated at 9/10 with no associated nausea or vomiting. The patient self-reported a history of peptic ulcer at age 16. He was not taking any prescription medications, but reported use of 10 ibuprofen 200 mg tablets every 2-3 days and 20-30 aspirin 325 mg tablets a week for back pain and "sinus problems". He also reported a history of smoking 2-3 cigars per day.

The physical examination was remarkable for hypoactive bowel sounds, diffuse abdominal tenderness, and guarding. An abdominal computed tomography (CT) scan revealed pneumoperitoneum consistent with perforated viscus. Exploratory laparotomy revealed a perforated duodenal ulcer which was repaired with a Graham patch (Omental patch).

On post-operative day (POD) 1, the patient displayed signs of sepsis (pulse 96, respiratory rate 25, white blood cell count 13.1 K/cm^3) and progressive hypoxemia. A chest x-ray demonstrated diffuse alveolar infiltrates. Attempts at non-invasive positive pressure ventilation failed and he was intubated subsequently on POD 2. At that time, the differential diagnosis included congestive heart failure and ARDS secondary to sepsis, gastric aspiration, and/or pneumonia. Normal echocardiogram and serum brain natriuretic peptide (BNP) excluded chronic heart failure. As a result, lung protective ventilation (tidal volume 6 mL per kilogram of predicted body weight and a plateau pressure of 30 cm of water or less) was initiated in accordance with the ARDS Network.[11]

Despite low tidal volume ventilation and empiric broad spectrum antibiotics on POD 3, the patient had a PaO_2/FiO_2 of 118, and the decision was made to initiate neuromuscular blockade to facilitate mechanical ventilation and improve oxygenation. The patient was sedated with midazolam and fentanyl to a Ramsey score of 6 and bolused with a 15 mg loading dose of cisatracurium, followed by a 37.5 mg per hour continuous infusion for 48 hours. Train of four (TOF) monitoring was conducted intermittently throughout the duration of neuromuscular blockade. His doses would have been 11.7 mg and 2.3 mg/hr, respectively, if the 77.7 kg patient had been bolused and a drip started based on the low end dosage given in the package insert.

The infusion was diluted to a concentration of 1 mg/mL, resulting in the total administration of 1,815 mg of cisatracurium in 1,815 mL of 0.9% sodium chloride. Five minutes prior to initiation of the cisatracurium infusion, a TOF

measurement at the wrist revealed 4/4 twitches. TOF measurements taken 15 minutes, 30 minutes, one hour, and two hours after initiation of the infusion all resulted in a TOF of 4/4 twitches. Monitoring of TOF's conducted at 8 hours and 18 hours after the initiation of the infusion both revealed 0/4 twitches, indicating the achievement of 100% neuromuscular blockade.

When it was clear that thorough neuromuscular blockade had been achieved, TOF measurements were stopped per the previous study protocol as well as the lack of dosage adjustments. The patient received fentanyl and midazolam throughout the duration of paralysis. Shortly after 48 hours, the cisatracurium infusion was discontinued and the patient began to recover full neuromuscular function slowly. Within two hours, the patient was able to open his eyes and follow commands to squeeze an examiner's hand. Roughly seven hours after the cessation of the infusion, the patient was neurologically intact. Figure 1 highlights the observed change in the patients PaO_2/FiO_2 associated with the cisatracurium infusion.

The patient was extubated on POD 9, four days after the cessation of the cisatracurium infusion. His hospital stay subsequently was complicated by *clostridium difficile* infection for which treatment with metronidazole was administered. The patient was discharged on POD 23 to a skilled nursing facility.

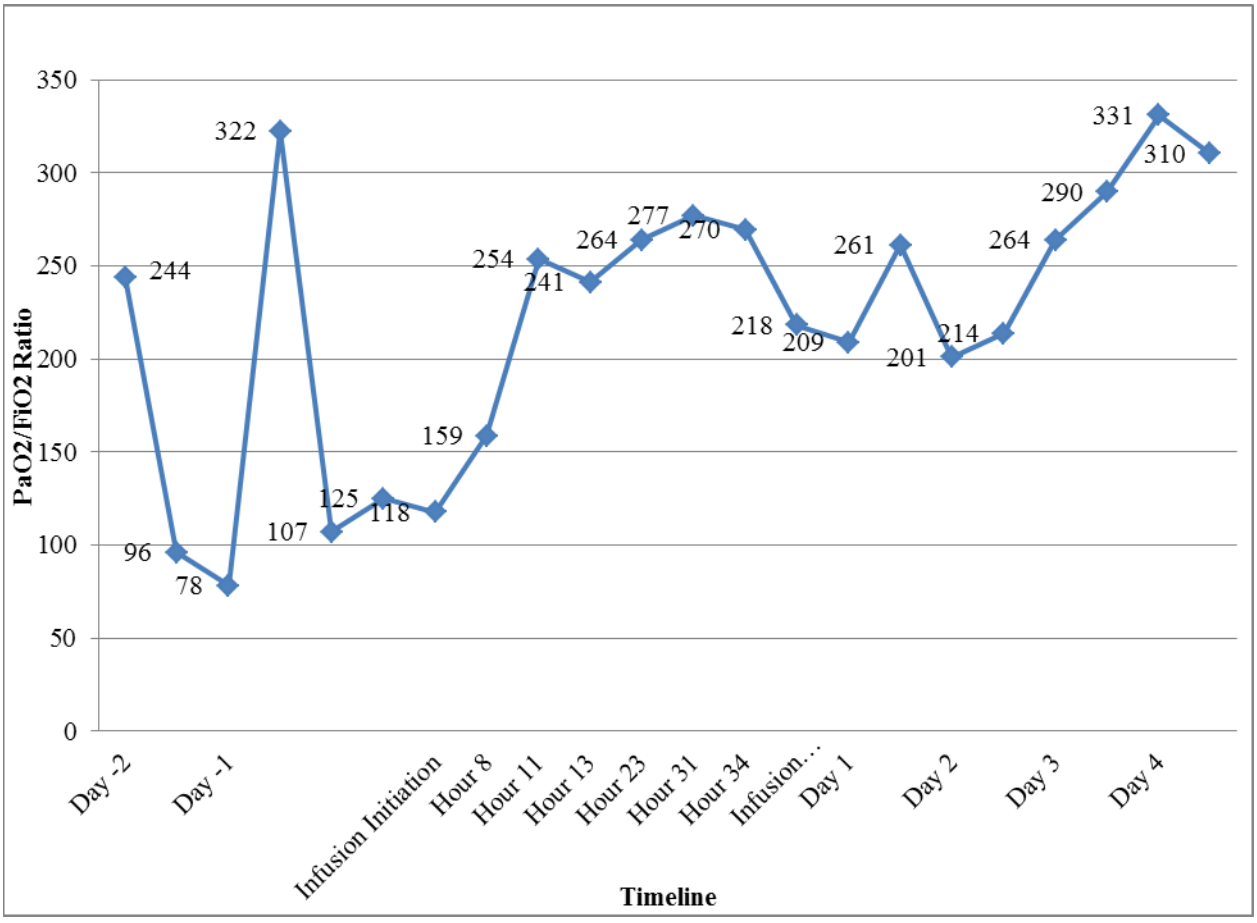


Figure 1. PaO2/FiO2 ratio.

Discussion

The dose of cisatracurium employed in this case was based on that used in the Papazian trial: a 15-mg bolus followed by a 37.5 mg per hour, 48-hour continuous infusion.[9] As displayed in Figure 1, the patient displayed rapid improvements in oxygenation corresponding with the cisatracurium administration. Improvement in the patient's PaO_2/FiO_2 of 100 (118 to 218) from infusion initiation to infusion termination were observed. Multiple measurements during the infusion also displayed even greater improvements in oxygenation than the final value obtained, with a peak value of 277. The cisatracurium infusion appeared to be a turning point toward clinical improvement in this patient. No other interventions such as prone positioning, inhaled nitric oxide, or epoprostenol were administered to the patient at any point during the treatment course. An outlier PaO_2/FiO_2 value was observed the day prior to cisatracurium initiation when a weaning trial was attempted. The post-cisatracurium period also consisted of continued improvement in oxygenation, despite the patient's overall complicated clinical picture.

Train of four monitoring via a peripheral nerve stimulator was used throughout the 48-hour period to assess neuromuscular blockade although it was not used to titrate the neuromuscular blocking agent. The Papazian study did not allow TOF monitoring to ensure proper blinding, however, in this case it was determined that TOF monitoring would be performed to assess effectiveness of neuromuscular blockade at set dose.[9] The patient's first four TOF measurements during the first two hours of the infusion displayed 4/4 twitches. This was an unexpected observation that is not explained readily. The TOF values obtained mid-infusion resulting in 0/4 twitches, suggested that neuromuscular blockade was effective. Prolonged blockade and muscle weakness are two primary concerns associated with NMBA infusion, however, this patient displayed no issues pertaining to either parameter. The patient regained motor function after cessation of the infusion and was considered neurologically normal within seven hours.

In the future, weight-based dosing titrated to a train of four response of 0/4 twitches could be considered to minimize cumulative exposure to cisatracurium and prevent possible adverse events associated with prolonged neuromuscular blockade or ICU acquired myopathies or polyneuropathies. Dose reductions could prove to be beneficial in terms of cost-savings due to medication acquisition costs and medication backorders due to drug shortages. To use this 77.7 kg patient as an example, his dosing range based on the standard administration rates would have been anywhere from 2.3 mg/hr to 46.6 mg/hr. The administered dose of 37.5 mg/hr, while in the dosage range, is on the higher end and positive outcomes may have been achievable with less medication. Diluting the concentration of the infusion to 1 mg/mL resulted in an increased volume administered, however, this was helpful in reducing confusion with regards to administration rates and dosing. With further practice and increased comfort, it may be preferable to administer this infusion undiluted, given that ARDS is an edematous disease state and conservative fluid administration is recommended.[12] This patient displayed a consistently positive fluid balance of +2,403 mL on the day of initiation, +1,152 mL during the first day, and +1,458 mL during the second day. For the treatment of this patient, just as in the cited studies, cisatracurium was utilized exclusively.[7-9] Future studies may be conducted to determine if the beneficial

effects observed are a result of an NMBA class effect or are exclusive to cisatracurium.

Conclusion

In summary, this case of a 60-year-old Caucasian male with ARDS was treated successfully with a 48-hour continuous infusion of cisatracurium, resulting in oxygenation improvement as measured by PaO_2/FiO_2. Cisatracurium may have resulted in recovery from ARDS and long-term survival. Based on these results coupled with the available literature, cisatracurium appears to be a safe and viable therapeutic option for patients with Acute Respiratory Distress Syndrome.[7-10]

References

[1] Johnson ER, Matthay MA. Acute lung injury: Epidemiology, pathogenesis, and treatment. J Aerosol Med Pulm D 2010; 23(4):243-252. PMID: 20073554.

[2] The ARDS Definition Task Force. Acute respiratory distress syndrome: The Berlin Definition. JAMA 2012; 307(23):2526-2533. PMID: 22797452.

[3] Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. N Engl J Med 2005; 353(16):1685-1693. PMID: 16236739.

[4] Erickson SE, Martin GS, Davis JL, Matthay MA, Eisner MD, NIH NHLBI ARDS Network. Recent trends in acute lung injury mortality: 1996-2005. Crit Care Med 2009; 37(5):1574-1579. PMID: 19325464.

[5] MacCallum NS, Evans TW. Epidemiology of acute lung injury. Curr Opin Crit Care 2005; 11(1):43-49. PMID: 15659944.

[6] Nimbex [package insert]. North Chicago, IL: Abbot Laboratories, November 2010.

[7] Gainnier M, Roch A, Forel JM, et al. Effect of neuromuscular blocking agents on gas exchange in patients presenting with acute respiratory distress syndrome. Crit Care Med 2004; 32(1): 113-119. PMID: 14707568.

[8] Forel JM, Roch A, Marin V, et al. Neuromuscular blocking agents decrease inflammatory response in patients presenting with acute respiratory distress syndrome. Crit Care Med 2006; 34(11): 2749-2757. PMID: 16932229.

[9] Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010; 363(12):1107-1116. PMID: 20843245.

[10] Alhazzani W, Alshahrani M, Jaeschke R, et al. Neuromuscular blocking agents in acute respiratory distress syndrome: A systematic review and meta-analysis of randomized controlled trials. Critical Care 2013; 17(2):R43. PMID: 23497608.

[11] The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000; 342(18):1301-1308. PMID: 10793162.

[12] National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Comparison of two fluid mangement strategies in acute lung injury. N Eng J Med 2006; 354(24):2564-2575. PMID: 16714767.

Keywords: cisatracurium, Acute Respiratory Distress Syndrome, neuromuscular blockade

Follicular Lymphoma of the GI Tract

Said Chaaban, M.D.,
Mustapha El-Halabi, M.D.,
William J. Salyers, Jr., M.D., M.P.H.
University of Kansas
School of Medicine-Wichita
Department of Internal Medicine

Introduction

Forty percent of follicular lymphomas in the United States are non-Hodgkin lymphomas.[1] The presentation is usually nodal; extra-nodal involvement is rare. The most common extra-nodal involvement is the gastrointestinal (GI) tract. We present a patient who presented with recurrent episodes of partial small bowel obstruction secondary to a primary follicular lymphoma of the GI tract.

Case Report

A 57-year-old female with a history of fibromyalgia presented with recurrent episodes of partial small bowel obstruction recurring every 2 to 8 weeks, and lasting for up to 3 days. Her episodes started two years prior after she underwent surgery for release of an internal hernia secondary to adhesions as well as an incidental appendectomy. One year later, her symptoms recurred. They usually started with abdominal pain, progressing to nausea and vomiting, and ultimately resolving spontaneously. She denied weight change, change in bowel habits, melena, hematochezia, fevers, chills, or night sweats.

An exploratory laparotomy was performed to reveal any pathology that would explain the symptoms. As it was non-revealing, an esophagogastroduodenoscopy was performed, but it also was benign. A colonoscopy showed the presence of collagenous colitis, but it required no treatment. Finally, a capsule endoscopy revealed an ulcerated area and stricture in the distal ileum, followed by double balloon enteroscopy with findings suggestive of grade A esophagitis and an ulcerated strictured mucosa in the proximal to mid ileum which was biopsied and tattooed (Figure 1). Pathology was non-diagnostic.

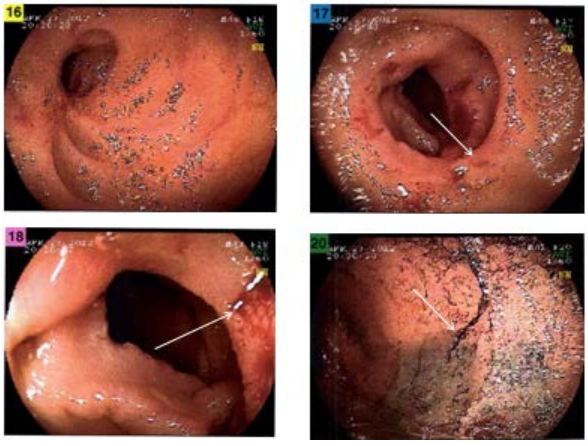


Figure 1. Images taken during double balloon enteroscopy revealing ulcerated strictured mucosa in the proximal to mid ileum.

In view of the patient's continuous problems, she underwent small bowel resection of the tattooed section. Immunophenotypes were positive for CD 20 (Figure 2), BCL-2 (Figure 3), and BCL-6 (Figure 4) with a Ki-67 of 20% and negative for cyclin B1, CD 3 and CD 5.

Immunohistochemical stains on the regional lymph nodes were reactive and not involved in the lymphoma, thus the diagnosis was consistent with stage 1E primary follicular lymphoma.

The patient had a follow-up PET scan that was negative for any suspicious hypermetabolic mass or adenopathy. Her management was mainly observation with follow-up PET scans. She improved with no evidence of recurrence.

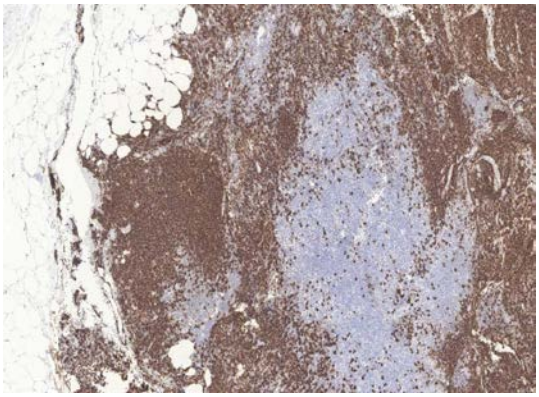


Figure 2. Immunophenotypic staining of the surgical specimen (CD 20).

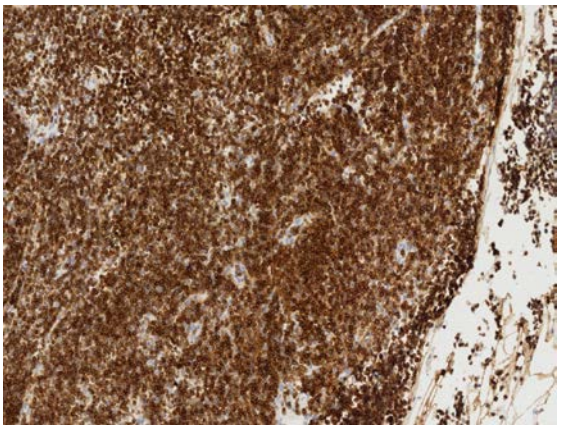


Figure 3. Immunophenotypic staining of the surgical specimen (BCL-2).

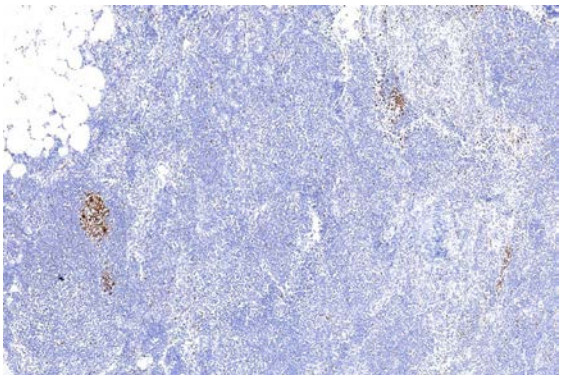


Figure 4. Immunophenotypic staining of the surgical specimen (BCL-6).

Discussion

The most common primary gastrointestinal lymphoma is marginal zone lymphoma.[2] Risk factors for the development of GI lymphomas include H. pylori infections, immunosuppression, inflammatory gastrointestinal diseases, and HIV. Primary follicular lymphoma was first described in 1997.[3] It is rare and constitutes 1% to 3.6% of all GI lymphomas.[2] Primary follicular lymphoma is more prevalent amongst females and the average age at diagnosis is 56 years. Until 2010, 249 cases were reported in the literature; half were in Japan.

Mucosa-associated lymphoid tissue (MALT) lymphoma differs from nodal marginal zone lymphoma as it usually arises in organs that lack lymphoid tissues but accumulates B-cells in response to chronic inflammation. It may arise in the stomach, lung, ocular adnexa, or salivary gland and is associated with gastroduodenitis caused by Helicobacter Pylori.[4] Patients are usually asymptomatic; 10% of cases present with vague gastrointestinal symptoms.[2] The most common GI symptoms include abdominal pain, nausea and vomiting, and GI bleed. The absence of palpable lymphadenopathy in the chest and abdomen based on imaging and sole involvement of the GI tract with a normal white cell count and differential are needed for diagnosis. Immunophenotype of

the tumor cells are B cells, and it tests negative for CD43, CD5, D1 and cyclin.

Gastrointestinal lymphoma is usually unifocal, but with the increase in use of capsule endoscopy, there have been more reports with regards to multifocal disease.[2] The second portion of the duodenum is involved most commonly, followed by the terminal ileum, stomach, and rarely the colon and rectum. LeBrun et al.[5] hypothesized that those neoplasms had a predilection to the terminal ileum because of the relatively abundant lymphoid tissue, Peyer's patches, that are prevalent in the small intestine.

Similar to other gastrointestinal malignancies, the gross appearance of GI lymphoma relates to the site of involvement. It appears as ulcers in the stomach, an obstructing mass in the small intestine, or polyps in the colon.[1,5] Surgical removal is almost impossible because of the large involvement of the viscus. Spread to regional and distant lymph nodes, liver, spleen, and bone marrow may occur at later stages.[5] Differential diagnosis of primary follicular lymphoma based on histology includes follicular lymphoid hyperplasia, GI involvement from follicular lymphomas originating from nearby lymph nodes, primary marginal zone lymphomas, and lymphomatous polyposis.[2]

Examination of the small bowel is challenging. Current modalities include enteroclysis, push enteroscopy, and capsule endoscopy.[6] Capsule endoscopy, first introduced in 2000, is a procedure to visualize the entire small bowel. Capsule endoscopy identifies lymphomas more than what was hypothesized previously and serves as a good modality for assessing success of treatment. Double balloon enteroscopy was shown to be an invaluable tool for diagnosis of diminutive small bowel lesions, but was a recommended procedure for the extensive staging of primary follicular lymphomas.[7] Video capsule endoscopy should be used initially as a screening procedure and follow-up, whereas double balloon enteroscopy should be added to the examination prior to the initiation of the treatment.[8]

There have been no prospective randomized clinical trials that elucidate optimal treatment modalities for non-Hodgkin lymphoma. Management ranges from surgery, if the patient has obstructive symptoms, to radiation and chemotherapy.[1] The CHOP regimen with rituximab has been shown to be effective in complete regression of the neoplasm during an early stage.[8] Survival in those patients ranges from 10 to 16 years and treatment is individualized.[2] Patients usually have an indolent course and a favorable outcome.[1,9,10]

Our case alerts physicians, particularly gastroenterologists, to consider the diagnosis of follicular lymphoma as one with a favorable outcome despite it being rare. This case highlighted the need of both capsule endoscopy and double balloon enteroscopy in reaching the diagnosis, however, in rare cases, the need for surgical resection is warranted to establish the diagnosis.

References

[1] Shia J, Teruya-Feldstein J, Pan D, et al. Primary follicular lymphoma of the gastrointestinal tract: A clinical and pathologic study of 26 cases. Am J Surg Pathol 2002; 26(2):216-224. PMID: 11812943.

[2] Juan Carlos Hiromi López T, María del Pilar Casasbuenas D, Jinneth Acosta F, Orlando Ricaurte G. Primary follicular lymphoma of the duodenum: Case report and literature review. Rev Col Gastroenterol 2012; 27(3): 215-220.

[3] Misdraji J, Fernandez del Castillo C, Ferry JA. Follicle center lymphoma of the ampulla of Vater presenting with jaundice: Report of a case. Am J Surg Pathol 1997; 21(4):484-488. PMID: 9130997.
[4] Thieblemont C, Bertoni F, Copie-Bergman C, Ferreri AJ, Ponzoni M. Chronic inflammation and extra-nodal marginal-zone lymphomas of MALT-type. Semin Cancer Biol 2014; 24:33-42. PMID: 24333758.
[5] LeBrun DP, Kamel OW, Cleary ML, Dorfman RF, Warnke RA. Follicular lymphomas of the gastrointestinal tract. Pathologic features in 31 cases and bcl-2 oncogenic protein expression. Am J Pathol 1992; 140(6):1327-1335. PMID: 1376556.
[6] Flieger D, Keller R, May A, Ell C, Fischbach W. Capsule endoscopy in gastrointestinal lymphomas. Endoscopy 2005; 37(12):1174-1180. PMID: 16329013.
[7] Matsumoto T, Nakamura S, Esaki M, et al. Double-balloon endoscopy depicts diminutive small bowel lesions in gastrointestinal lymphoma. Dig Dis Sci 2010; 55(1):158-165. PMID: 19241169.
[8] Akamatsu T, Kaneko Y, Ota H, Miyabayashi H, Arakura N, Tanaka E. Usefulness of double balloon enteroscopy and video capsule endoscopy for the diagnosis and management of primary follicular lymphoma of the gastrointestinal tract in its early stages. Dig Endosc 2010; 22(1):33-38. PMID: 20078662.
[9] Sapoznikov B, Morgenstern S, Raanani P, et al. Follicular lymphoma with extensive gastrointestinal tract involvement: Follow-up by capsule endoscopy. Dig Dis Sci 2007; 52(4):1031-1035. PMID: 17353993.
[10] Huang WT, Hsu YH, Yang SF, Chuang SS. Primary gastrointestinal follicular lymphoma: A clinicopathologic study of 13 cases from Taiwan. J Clin Gastroenterol 2008; 42(9):997-1002. PMID: 18719510.

*Keywords***:** follicular lymphoma, capsule endoscopy, double-balloon enteroscopy

Antiphospholipid Antibody Syndrome: Often a Conundrum in Clinical Practice

Vikram Panwar, M.D., M.P.H.[1], Brent Duran, D.O.[2], Amad U. Din, M.D., M.P.H.[3], George Martinez, M.D.[1,2]
[1]Robert J. Dole Veteran's Administration Medical Center, Wichita, KS
[2]University of Kansas School of Medicine-Wichita Department of Internal Medicine
[3]University of Kansas School of Medicine-Kansas City Department of Psychiatry and Behavioral Sciences

Introduction

Thrombosis is one of the common causes for hospital admission and emergency room visits.[1] Thrombosis is associated with significant morbidity and mortality. Hypercoagulability is a condition characterized by tendency to have thrombosis as a result of inherited and/or acquired defects.

The prevalence of hypercoagulable state is low in the general population but is greater in people with genetic predisposition.[2] Antiphospholipid antibody syndrome (APS) accounts for approximately 28% of cases with hypercoagulability conditions, followed by activated protein C resistance (25%) and malignancy (15%).[1] Other conditions associated with hypercoagulability states include pregnancy and medications. Geographic variations have been reported in APS as follows: Sweden 15%, Cyprus 13% and the Middle East 5%.[3,4]

Clinicians must have a high index of suspicion for APS in patients with multiple thrombotic episodes, idiopathic DVT, or spontaneous abortions. An investigation for antiphospholipid antibodies early at presentation is important as it may influence the course of the disease.

We present a discussion of a case, where a patient initially had negative lab work-up for APS but had positive clinical features. He developed positive lab work-up for APS during later years and was managed with optimum anticoagulation therapy and education of the patient.

Case Report

A 57-year-old Caucasian male presented to the emergency department with complaints of right upper arm pain and erythema. The pain was acute in onset, radiating towards his palm, and rated as 5/10 (10 being the most severe pain) with no aggravating or relieving factors. For the prior month, the patient had intermittent pain in his right upper arm, but he did not seek medical treatment as the symptoms resolved spontaneously.

The patient had a history of multiple hospitalizations. The first one was in 1970 when he was admitted for deep vein thrombosis (DVT) and placed on warfarin for three months. After a hospitalization in 2003 for pulmonary embolism, he was placed on lifelong warfarin therapy. He was re-admitted to the hospital in 2003 for DVT. He had a negative work-up for APS in terms of following lab parameters: APTT, lupus anti-coagulant, cardiolipin screen, and hexagonal phospholipid test. In 2010, he was diagnosed with APS with the following lab parameters: APTT of 48 seconds, lupus anti-coagulant was positive, cardiolipin screen was negative, and hexagonal phospholipid test was positive. He

underwent a right above knee amputation in 2012 secondary to ischemia. He was non-compliant with his medications from 2010 to 2013. Also suspecting warfarin resistance due to non-compliance or due to decrease sensitivity of vitamin K 2,3-epoxide reductase to warfarin, he was switched from warfarin to enoxaparin. The patient's father also had a history of recurrent clots.

On physical exam, the patient's right upper extremity was cool to touch, capillary refill was greater than ten seconds, and a purple discoloration of the skin extended from his fingertips to mid forearm. There was an inability to palpate a radial, ulnar, or brachial pulse of the right upper extremity. The left upper extremity had diminished, but had palpable pulses. There was no pain to palpation of either extremity. No clubbing or edema of either upper extremity was noted. A peripheral angiogram showed thrombi in the right brachial artery extending into right radial artery. He subsequently underwent suction thrombectomy along with tissue plasminogen activator infusion to the clot. A follow-up angiogram showed a patent right brachial artery. He was placed on heparin for twenty-four hours, then switched to enoxaparin sodium, and finally bridged to warfarin successfully.

At the time of his recent admission, lab values included hemoglobin of 12.9 g/L, white blood count of 11,100 cells/mcL, mean corpuscular volume of 93.8 fL, glucose of 90 mg/dL, creatinine of 0.96 mg/dL, fibrinogen of 390, INR of 1.1, and activated partial thromboplastin time of 61 seconds. Labs on discharge included hemoglobin of 12.3 g/L, creatinine of 0.87 mg/dL, blood urea nitrogen of 9 mg/dL, activated partial thromboplastin time of 25.5 seconds, prothrombin time of 10, and INR of 2.5. He was advised on discharged to continue warfarin of 5 mg per day, enoxaparin 120 mg per day, and atenolol of 50 mg per day, and follow-up with the surgical vascular clinic. His INR goal was set at 2.5-3.0. He was educated about the importance of being compliant with his management and follow up visits at time of discharge.

Discussion

APS is an autoimmune disease characterized clinically by hypercoagulable state.[4] Its diagnosis is confirmed by the presence of at least one type of antibody (lupus anticoagulant, anti-cardiolipin antibody, or anti-β2-glycoprotein-I anti-bodies) in the plasma, and the occurrence of at least one of the following clinical manifestations: venous or arterial thrombosis, or pregnancy morbidity[5] (see classification criteria in appendix). The antibodies are directed not only against the epitopes on plasma proteins that are uncovered or generated by the binding of these proteins to phospholipids, but also to phospholipid binding proteins.[6] Anti-phospholipid antibodies (aPL) can disturb both pro- and anticoagulant pathways. Screening for these antibodies should include at least two phospholipid dependent coagulation tests: activated partial thromboplastin time, diluted prothrombin time, and diluted Russell viper venom time to increase specificity (identify true negatives).[7] A mixing test should be done following abnormal screening and failure of correction of clotting time should be confirmed by demonstration of phospholipid dependence of the inhibitor (hexagonal phospholipid ethanolamine time).[8]

The exact pathogenesis of APS is unknown. However, proposed hypotheses include activation of endothelial cells by antiphospholipid antibodies, interference with functioning of phospholipid binding proteins involved in coagulation, or oxidant-mediated injury of vascular endothelium.[9] These antiphospholipid antibodies can be formed in the susceptible individual

secondary to infections, autoimmune disorders such as systemic lupus erythematosus or rheumatic disorder, or malignancy, such as colon cancer, prostate cancer, or leukemia leading to APS.[10,11] These antibodies bind to endothelial cells causing stimulation of adhesion molecule and creating a pro-thrombotic state.[9] Close association exists between systemic lupus erythematous and APS.[12,13] Keeling et al.[7] reported that patients with systemic lupus erythematosus who were lupus anticoagulant positive had a six times greater risk of having a thromboembolic event as compared to patients who were negative. Similarly, those with a positive cardiolipin antibody had twice the risk.

Given the broad clinical presentation of APS, primary and secondary prevention for thrombosis is crucial. However, two prospective randomized trials reported that recurrences of vascular event in a low intensity treatment group (INR of 2-3) was less as compared to those in the high intensity group (INR of 3.1-4).[14] Schluman et al.[15] and Kearon et al.[16] reported that the rate of recurrence of a thrombotic event is less if therapy is given for a longer duration of time. In both studies, bleeding was more in the high intensity group (INR 3.5-4). The Antiphospholipid Antibody and Stroke Study (APASS) showed aspirin (325 mg/day) and low-to-moderate anticoagulation were equally effective in patients with initial stroke irrespective of their antiphospholipid antibody status.[17] The current recommendation for the management for APS or DVT is to have a therapeutic INR of 2.5-3. The duration of therapy depends per individual case and the risk/benefit ratio.[14] Annual risk of bleeding within a therapeutic INR of 2-3 is 2%.[9]

The American College of Chest Physicians Guidelines[18] for arterial thrombosis is to treat with aspirin or low-to-moderate intensity anticoagulation (INR of 1.5-2.5). For cancer associated with DVT or pulmonary embolism, clinicians should treat for at least 3-6 months and preferably with long-term anticoagulation therapy, unless bleeding risk is very high. A pregnant patient with a history of recurrent pregnancy loss (< 10 weeks) should be screened for antiphospholipid antibodies. If positive, low molecular weight heparin and aspirin should be given throughout pregnancy. If there is a history of pre-eclampsia, low dose aspirin is recommended. If the thrombotic event recurs during warfarin therapy, despite INR levels that are within the target range of 2.0 to 3.0, then an alternate treatment could be low molecular weight heparin or anti-Xa therapy.

APS is present if at least one of the following clinical criteria and one of the laboratory criteria are met.[4] For vascular thrombosis, episodes of arterial, venous, or small vessel thrombosis must be present in any tissue or organ or plasma on two or more occasions at least 12 weeks apart. Thrombosis must be confirmed by objective and validated criteria (i.e., unequivocal findings of appropriate imaging studies or histopathology). For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.

For pregnancy morbidity, either one of three conditions must be present.[5] They include: (1) one or more unexplained deaths of a morphologically normal fetus at or beyond the 10^{th} week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, (2) one or more premature births of a morphologically normal neonate before the 34^{th} week of gestation because of eclampsia or severe pre-eclampsia defined according to standard definitions, or recognized features of placental insufficiency, or (3) three or more unexplained consecutive spontaneous abortions before the 10^{th} week of gestation,

with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes have been excluded.

Laboratory criteria for APS includes: (1) lupus anticoagulant (LA) present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis (Scientific Subcommittee on LAs/phospholipid-dependent antibodies)[17], (2) anticardiolipin (aCL) antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (i.e., > 40 GPL or MPL, or greater than the 99th percentile), on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA, (3) anti-β_2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma (in titer greater than the 99th percentile), present on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA, according to recommended procedures.

Conclusion

Anti-phospholipid antibody syndrome is a pro-thrombotic condition but with varied clinical presentation.[19] Therefore, treatment needs to be individualized depending on the clinical presentation. Education regarding medication administration is essential. More research is required to understand the patho-physiology of this syndrome, to validate the criteria, and to identify optimal treatment.[20,21]

References

1 Thomas RH. Hypercoagulability syndromes. Arch Intern Med 2001; 161(20):2433-2439. PMID: 11700155.

2 Rosendaal FR. Risk factors for venous thrombosis: Prevalence, risk, and interaction. Semin Hematol 1997; 34(3):171-187. PMID: 9241704.

3 De Stefano V, Chiusolo P, Paciaroni K, Leone G. Epidemiology of factor V Leiden: Clinical indications. Semin Thromb Hemost 1998; 24(4):367-379. PMID: 9763354.

4 Levine JS, Branch DW, Rauch J. The antiphospholipid syndrome. New Engl J Med 2002; 346(10):752-763. PMID: 11882732.

5 Luma HN, Doualla MS, Temfack E, Bagnaka SA, Mankaa EW, Fofung D. The antiphospholipid antibody syndrome: A case report. Int Med Case Rep J 2012; 5:63-67. PMID: 23754926.

6 Kandiah DA, Krilis SA. Beta 2-glycoprotein I. Lupus 1994; 3(4):207-212. PMID: 7804302.

7 Keeling D, Mackie I, Moore GW, et al. Guidelines on the investigation and management of antiphospholipid syndrome. Br J Haematol 2012; 157(1):47-58. PMID: 22313321.

8 Giannakopoulos B, Passam F, Ioannou Y, Krilis SA. How we diagnose the antiphospholipid syndrome. Blood 2009; 113(5):985-994. PMID: 18755986.

9 Pierangeli SS, Colden-Stanfield M, Liu X, Barker JH, Harris EN. Antiphospholipid antibodies from antiphospholipid syndrome patients activate endothelial cells in vitro and in vivo. Circulation 1999; 99(15):1997-2002. PMID: 10209004.

10 Karassa FB, Ioannidis JP, Touloumi G, Boki KA, Moutsopoulos HM. Risk factors for central nervous system involvement in systemic lupus erythematosus. QJM 2000; 93(3):169-174. PMID: 10751236.

11 Cervera R, Asherson R, Acevedo ML, et al. Antiphospholipid syndrome associated with infections: Clinical and microbiological characteristics of 100 patients. Ann Rheum Dis 2004; 63(10):1312-1317. PMID: 15361392.

[12] Zandman-Goddard G, Chapman J, Shoenfeld Y. Autoantibodies involved in neuropsychiatric SLE and antiphospholipid syndrome. Semin Arthritis Rheum 2007; 36(5):297-315. PMID: 17258299.

[13] Schulman S, Svenungsson E, Granqvist S. Anticardiolipin antibodies predict early recurrence of thromboembolism and death among patients with venous thromboembolism following anticoagulant therapy. Duration of the Anticoagulation Study Group. Am J Med 1998; 104(4): 332-338. PMID: 9576405.

[14] Khamashta MA, Cuadrado MJ, Mujic F, Taub NA, Hunt BJ, Hughes GR. The management of thrombosis in the antiphospholipid-antibody syndrome. N Engl J Med 1995; 332(15):993-997. PMID: 7885428.

[15] Schulman S, Rhedin AS, Lindmarker P, et al. A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism. Duration of Anticoagulation Trial Study Group. N Engl J Med 1995; 332(25):1661-1665. PMID: 7760866.

[16] Kearon C, Gent M, Hirsh J, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. N Engl J Med 1999; 340(12):901-907. PMID: 10089183.

[17] Lim W. Antiphospholipid antibody syndrome. Hematology Am Soc Hematol Educ Program 2009; 233-239. PMID: 20008203.

[18] Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141(2 Suppl):e154S-e184S. PMID: 22315259.

[19] Pierangeli SS, Chen PP, Raschi E, et al. Antiphospholipid antibodies and the antiphospholipid syndrome: Pathogenic mechanisms. Semin Thromb Hemost 2008; 34(3):236-250. PMID: 18720303.

[20] Lim W, Crowther MA, Eikelboom JW. Management of antiphospholipid antibody syndrome: A systematic review. JAMA 2006; 295(9):1050-1057. PMID: 16507806.

[21] Giannakopoulos B, Krilis S. How I treat the Antiphospholipid Syndrome. Blood 2009; 114(10):2020-2030. PMID: 19587374.

[22] Kearon C, Kahn SR, Agnelli G, et al. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133(6 Suppl):454S-545S. PMID: 18574272.

Keywords: antiphospholipid syndrome, autoantibodies, thrombosis, case report

Appendix

Revised Classification Criteria for the Antiphospholipid Antibody Syndrome[22]

Clinical criteria (one or more)

1. Vascular thrombosis: One or more objectively confirmed episodes of arterial, venous or small vessel thrombosis occurring in any tissue or organ.
2. Pregnancy morbidity: a) one or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation; or b) one or more premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia, pre-eclampsia or placental insufficiency; or c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation.

Laboratory criteria: (one or more, present on 2 or more occasions at least 12 weeks apart using recommended procedures)

1. Lupus anticoagulant, detected according to the guidelines of the International Society on Thrombosis and Haemostasis.
2. Anticardiolipin antibody of IgG and/or IgM isotype, present in medium or high titer (greater than 40 GPL or MPL, or greater than the 99th percentile), measured by a standardized ELISA
3. Anti-β2-glycoprotein-1 antibody of IgG and/or IgM isotype, present in titer greater than the 99th percentile, measured by an ELISA.

Current evidence-based guidelines for treatment[18, 22]

1. Venous Thrombosis
   Distal leg DVT:
   a) Severe symptoms: Treat with anticoagulants for three months
   b) No/mild/moderate symptoms: No anticoagulation needed

   Proximal leg DVT
   a) 3 months, unless idiopathic (long term)

   Cancer associated DVT or PE
   a) Treat for at least 3 months and preferably long-term, unless bleeding risk very high

   Arterial Thrombosis
   a) Aspirin or low/ moderate intensity anticoagulation (INR 1.5-2.5)
   b) In patients with atrial fibrillation; warfarin or aspirin + clopidogrel

It is recommended in the guidelines that patients who have had a first unprovoked (idiopathic/genetic) proximal DVT or pulmonary embolism be considered for long-term anticoagulation, independent of considerations such as the presence or absence of an identifiable genetic or acquired thrombophilia.[22] If the patient develops another event while being on warfarin or aspirin, there is evidence that they should be put on warfarin with higher INR or warfarin with aspirin.[18, 22]

Primary Pleomorphic Adenoma of the Lung

Tanyaradzwa M. Kajese, M.D.[1]
Sanjay G. Khicha, M.D.[1,2]
Gyanchand J. Khicha, M.D.[1,2]
[1]University of Kansas School of Medicine-Wichita, Department of Surgery
[2]Via Christi Hospital Saint Francis, Department of Surgery, Wichita, KS

Introduction

Despite being the most common type of benign salivary gland lesion, pleomorphic adenomas are encountered rarely as primary pulmonary tumors. Fewer than twenty cases have been presented in the literature.[1-5] When described in the lung, these tumors tend to be centrally located and associated with a major or secondary bronchus.[1,4,5] Since they are so rare, there is no standard-of-care for the treatment of these lesions. However, similar to their salivary gland counterparts, the consensus is to resect them surgically with clear margins. Their incomplete excision may be associated with local recurrence.[1] We present a rare benign pulmonary tumor that was diagnosed as a primary pleomorphic adenoma.

Case Report

A 61-year-old woman was evaluated in the outpatient setting for a new lung mass. With a previous history of breast cancer, the patient underwent a routine chest x-ray that illustrated a right-sided lung density. On computed tomography (CT) scan of the chest, there was a 3.5 cm hilar mass associated with post-obstructive atelectasis (Figure 1). Aside from breast cancer, she denied any other medical co-morbidities. She had never smoked and had no symptoms of weight loss, chest pain, dyspnea, cough, or hemoptysis. She had no salivary gland symptoms such as mandibular pain, swelling, or facial nerve palsy. Her physical examination was unremarkable.

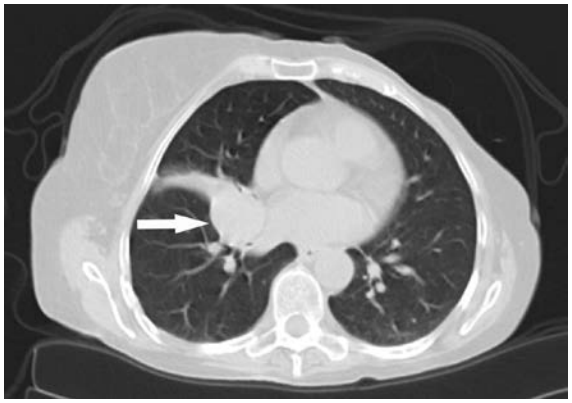


Figure 1. CT scan of the chest illustrating a 3.5 cm right hilar mass (arrow).

On initial work-up, peripheral blood counts were normal. A full body positron emission tomography (PET) scan showed hyper-metabolism in the right hilum with a standard uptake value of 5.1 consistent with the location of the lesion noted on the CT scan. There were no other regions of hyper-metabolism, including the salivary glands. Additionally, there was no evidence of mediastinal adenopathy. Because of its proximity to and involvement of the right hilum, a bronchoscopy with biopsy of the lesion was conducted. The pathology illustrated positive immunohistochemical staining for pankeratin, vimentin, smooth muscle actin, glial fibrillary acidic protein, and S-100. These findings substantiated the diagnosis of primary pulmonary pleomorphic adenoma.

Pulmonary function testing demonstrated: vital capacity (VC) = 3.26 L, %VC

= 98%, forced expiratory volume (FEV1) = 2.54L, %FEV1 = 103%, carbon monoxide diffusing capacity (DLCO) = 19.3mL/ mmHg/min, %DLCO = 104%. Surgical resection was recommended and a right posterolateral thoracotomy was performed. At the time of surgery, the tumor was found to encroach into the bronchus intermedius. A right middle and lower lobectomy had to be performed. The patient tolerated surgery without any complications.

The final pathology following her lobectomies illustrated a pleomorphic adenoma measuring 4.5 x 3 x 3 cm in size with invasion into the bronchus intermedius (Figure 2). The bronchial resection margin was free of tumor, and the six identified regional lymph nodes were free of invasion.

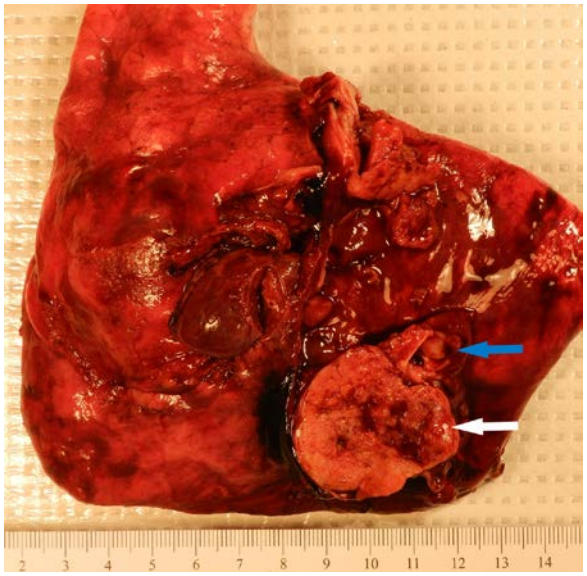


Figure 2. Photograph of the gross pathologic specimen illustrating the pleomorphic adenoma (white arrow) with invasion into the right bronchus intermedius (blue arrow).

The patient was dismissed from the hospital on post-operative day three. Her follow-up in the outpatient setting was continued with routine chest imaging because of her previous history of breast cancer. It also allowed for screening any possible recurrence of her pleomorphic adenoma. At eighteen months of follow-up, she was without complications or recurrence.

Discussion

Pleomorphic adenoma rarely presents as a primary pulmonary lesion. When it does, it typically arises from seromucous glands of the trachea and major bronchi.[3,5] Because of their rarity, the true incidence of these lesions is unknown. In addition, the prognosis of these tumors in this setting is unclear. They exhibit similar microscopic and immunohistochemical characteristics as those seen in salivary gland tumors.[3] In the absence of metastases, the current consensus is to treat these lesions with complete surgical resection, including negative margins. Long-term surveillance is recommended because of the possibility of local recurrence, which, as in the case of their salivary gland counterparts, may present years following surgical excision.[1] While long-term surveillance is recommended, there are no specific guidelines on the type or frequency of imaging.

This was a rare case of a primary pleomorphic adenoma of the lung in a patient who was asymptomatic. Tissue diagnosis was used to guide her overall treatment. The patient remained healthy without any further evidence of recurrence or surgical complications. The appreciation for the presence of these tumors in the lung allow for appropriate surgical therapy. It also provides an opportunity for more expansive dialogue that may lead to definitive standard-of-care guidelines for treatment and surveillance follow-up.

References

[1] Ang KL, Dhannapuneni VR, Morgan WE, Soomro IN. Primary pulmonary pleomorphic adenoma: An immuno-histochemical study and review of the literature. Arch Pathol Lab Med 2003; 127(5):621-622. PMID: 12708911.

[2] Carretta A, Libretti L, Taccagni G, Zannini P. Salivary gland-type mixed tumor (pleomorphic adenoma) of the lung. Interact Cardiovasc Thorac Surg 2004; 3(4):663-665. PMID: 17670335.

[3] Goto T, Maeshima A, Akanabe K, et al. Bronchial pleomorphic adenoma coexisting with lung cancer. Ann Thorac Cardiovasc Surg 2001; 17(2):174-177. PMID: 21597416.

[4] Jin HY, Park TS. Pulmonary pleomorphic adenoma: Report of a rare case. Korean J Intern Med 2007; 22(2):122-124. PMID: 17616030.

[5] Vargas SO. Pleomorphic adenoma of the lung. Available at: http://test.pathologyportal.org/site~/98th/specpedih1v.htm. Accessed May 9, 2013.

Keywords: lung, lung neoplasms, pneumonectomy, bronchial diseases, immunochemistry

Bortezomib in the Treatment of Acquired von Willebrand Disease Secondary to Monoclonal Gammopathy of Undetermined Significance

Kenneth Byrd, M.D.[1], Phu Truong, M.D.[1,2]
[1]University of Kansas School of Medicine-Wichita
Department of Internal Medicine
[2]Cancer Center of Kansas, Wichita, KS

Introduction

Acquired von Willebrand syndrome (AvWS) is a rare condition most commonly associated with the lymphoproliferative disorders, including monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma, and Waldenström's macroglobulinemia.[1-3] It is a disorder of von Willebrand factor (vWF) concentration, structure, or function that is not inherited directly but is a consequence of another medical disorder.[4] There are multiple mechanisms leading to AvWS: autoimmune clearance or inhibition of vWF, increased shear-induced proteolysis of vWF, or increased binding of vWF to platelets or other cell surfaces.[2,3,4] Autoantibodies commonly are implicated in AvWS associated with MGUS.[1,4,5] Thus, these patients often do not respond to standard von Willebrand disease (vWD) therapy.[6] This case provided evidence that bortezomib may be an option for patients refractory to standard AvWS therapy in the setting of MGUS.

Case Report

A 67-year-old female without prior personal or family history of a bleeding diathesis originally presented with acute gastrointestinal bleeding. She subsequently had recurrent episodes of epistaxis and gastrointestinal bleeding requiring multiple blood transfusions. An extensive workup revealed the diagnosis of AvWS. She was not on blood thinners or any other medications known to cause AvWS. Her von Willebrand antigen at diagnosis was low at 3.1 units, von Willebrand ristocetin cofactor was 6, and factor VIII activity was 10.7%. A short time later, she also was diagnosed with MGUS.

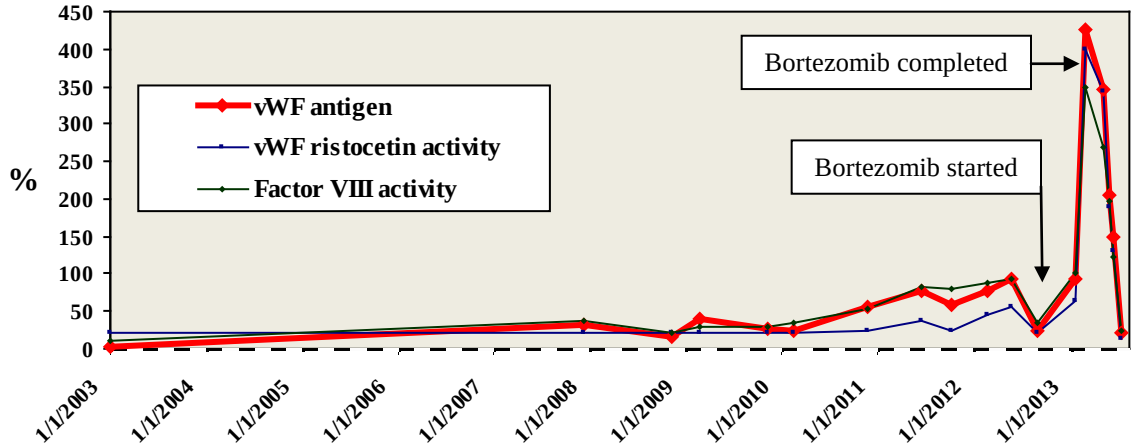
First line treatment with desmopressin was initiated, but the patient had severe nausea and her disease had very minimal response. She subsequently failed therapy with prednisone and vWF complex. Next, she was given four cycles of rituximab therapy with only minimal response. Even though the patient never had a confirmed vWF antibody, she was next treated empirically with intravenous immune-globulin (IVIG) monotherapy. She had good response to IVIG as evidenced by an increase in her vWF antigen, vWF ristocetin activity, and factor VIII activity.

Over the next nine years, the patient received IVIG infusions for two consecutive days every 2½ weeks. Her episodes of bleeding were decreased during this nine-year period, but she continued to have infrequent bleeding. She also had frequent headaches and nausea and another treatment strategy was explored.

Based on a published case report, bortezomib was added to the IVIG therapy.[7] Treatment included six cycles of bortezomib 2.5 mg on days one, four, eight, and 11 of a 21-day cycle.[7] Treatment with IVIG was continued during this four-month treatment period. During treatment, the patient had no

clinical bleeding and there was a remarkable increase in her vWF antigen, vWF activity, and factor VIII activity (Table 1). In addition, the MGUS monoclonal protein became undetectable. Once treatment with bortezomib and IVIG was stopped, remission was maintained for another two months, followed by relapse and an episode of gastrointestinal bleeding. The patient was not a candidate for additional bortezomib treatment due to drug-induced peripheral neuropathy. At that time, she resumed IVIG monotherapy which continued to be effective.

Table 1. Response of vWF antigen, vWF activity, and factor VIII activity during the 10-year treatment course of vWD.



Discussion

Similar to congenital vWD, the acquired syndrome can cause significant morbidity due to bleeding.[2] Unfortunately, standard vWD therapy is often ineffective for acquired von Willebrand syndrome.[5] These patients often do not respond to desmopressin or vWF replacement as there is frequently a circulating antibody that rapidly destroys the new circulating vWF.[5,6] Plasma antibodies to vWF are confirmed infrequently, but have been demonstrated by plasma mixing studies and functional assays.[4,6] In addition to antibodies, there is likely significant adsorption of the vWF to the increased circulating monoclonal cells. There is evidence of this occurring in multiple myeloma and it is possible that there is a similar mechanism involved in MGUS.[8]

Desmopressin produces at least short term improvement in only 32% of cases.[1] Factor replacement (vWF and FVIII) is also part of the standard vWD treatment, but has proven less effective in AvWS.[1,9] In patients who had a previous inadequate response to desmopressin and factor replacement, IVIG has some proven efficacy.[1,5,9] In one study, 33% of those who failed the first two therapies showed good response with IVIG.[1] Even if there is good clinical response, treatment with IVIG usually requires lifelong therapy that is both expensive and often difficult to tolerate. Other therapies such as plasmapheresis, antifibrinolytics, and rituximab have exhibited only marginal efficacy.[1,10,11]

In general, there appears to be minimal benefit to treating MGUS unless it

progresses to multiple myeloma.[12,13] However, there is insufficient evidence to guide the management of MGUS with other secondary complications, such as AvWS.[12] The standard approach to MGUS may be unsatisfactory when the patient has associated AvWS.

Bortezomib is a proteasome inhibitor commonly used in the treatment of multiple myeloma. It was shown in a prior case report to induce complete remission of both AvWS and MGUS.[7] Although the response was only short term in our case, bortezomib again appeared to have the potential to treat AvWS concurrent with MGUS effectively.

References

[1] Federici AB, Rand JH, Bucciarelli P, et al. Acquired von Willebrand syndrome: Data from an international registry. Thromb Haemost 2000; 84(2):345-349. PMID: 10959711.

[2] Veyradier A, Jenkins CS, Fressinaud E, Meyer D. Acquired von Willebrand syndrome: From pathophysiology to management. Thromb Haemost 2000; 84(2):175-182. PMID: 10959686.

[3] Tefferi A, Nichols WL. Acquired von Willebrand disease: Concise review of occurrence, diagnosis, pathogenesis, and treatment. Am J Med 1997; 103(6):536-540. PMID: 9428838.

[4] Nichols WL, Hultin MB, James AH, et al. von Willebrand disease (VWD): Evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel report (USA). Haemophilia 2008; 14(2): 171-232. PMID: 18315614.

[5] Federici AB, Stabile F, Castaman G, Canciani MT, Mannucci PM. Treatment of acquired von Willebrand syndrome in patients with monoclonal gammopathy of uncertain significance: Comparison of three different therapeutic approaches. Blood 1998; 92(8):2707-2711. PMID: 9763553.

[6] Mohri H, Motomura S, Kanamori H, et al. Clinical significance of inhibitors in acquired von Willebrand syndrome. Blood 1998; 91(10):3623-3629. PMID: 9572997.

[7] Ojeda-Uribe M, Caron C, Itzhar-Baikian N, Debliquis A. Bortezomib effectiveness in one patient with acquired von Willebrand syndrome associated to monoclonal gammopathy of undetermined significance. Am J Hematol 2010; 85(5):396. PMID: 20425807.

[8] Richard C, Cuadrado MA, Prieto M, et al. Acquired von Willebrand disease in multiple myeloma secondary to adsorption of von Willebrand factor by plasma cells. Am J Hematol 1990; 35(2):114-117. PMID: 2205095.

[9] Mohri H. Acquired von Willebrand syndrome: Features and management. Am J Hematol 2006; 81(8):616-623. PMID: 16823821.

[10] Kanakry JA, Gladstone DE. Maintaining hemostasis in acquired von Willebrand syndrome: A review of intravenous immunoglobulin and the importance of rituximab dose scheduling. Transfusion 2013; 53(8):1730-1735. PMID: 23252513.

[11] Tiede A, Rand JH, Budde U, Ganser A, Federici AB. How I treat the acquired von Willebrand syndrome. Blood 2011; 117 (25):6777-6785. PMID: 21540459.

[12] Kyle RA, Durie BG, Rajkumar SV, et al. Monoclonal gammopathy of undetermined significance (MGUS) and smoldering (asymptomatic) multiple myeloma: IMWG consensus perspectives risk factors for progression and guidelines for monitoring and management. Leukemia 2010; 24(6):1121-1127. PMID: 20410922.

[13] International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: A report

of the International Myeloma Working Group. Br J Haematol 2003; 121(5):749-757. PMID: 12780789.

Keywords: von Willebrand diseases, bortezomib, monoclonal gammopathy of undetermined significance

Pneumorrhachis

David J. Lerner, M.D.[1], Nikitha Potturi, MS1[1], Nebiyu Beteselassie, M.D.[2], Bruce Lerner, M.D.[2]
[1]University of Missouri-Kansas City School of Medicine, Kansas City, MO
[2]Truman Medicine Center Kansas City, MO

Introduction

Pneumorrhachis (PR) is a rare imaging finding characterized by the presence of air (either intra- or extra-dural) within the spinal canal.[1] It can be associated with different etiologies, such as iatrogenic, traumatic, and non-traumatic. Pneumorrhachis is typically asymptomatic and resolves spontaneously, making it difficult to detect. The varied pathogenesis of PR can make it a diagnostic challenge. In addition, the incidence of symptomatic PR is very rare. Therefore, there are no standard guidelines for the management of PR. Its treatment typically is individualized and requires a multi-disciplinary approach.

Case Report

A pregnant 27-year-old female presented for delivery. She had normal prenatal labs and clinical course. An epidural was performed. Delivery was without complication. The patient complained of diffuse vague abdominal pain the next day and subsequent abdominal cross-sectional imaging was performed with multiple reformatted images. Normal post-delivery changes were visualized in the abdomen. Incidentally, multifocal areas of air within the spinal canal were seen (Figures 1 and 2). The patient was afebrile, denied back pain, and had no elevated white cell count. Based upon her clinical history and physical exam, the diagnosis of iatrogenic pneumorrhachis was made. Follow-up exam revealed resolution of intra-spinal air. She went home a few days later without problem.

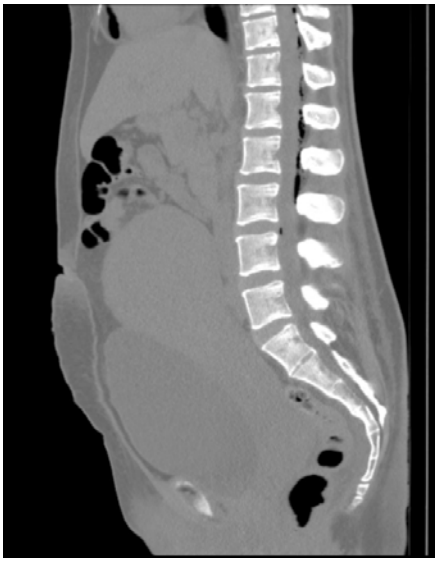


Figure 1. Sagittal non-contrast CT shows multilevel foci of air within the spinal canal.

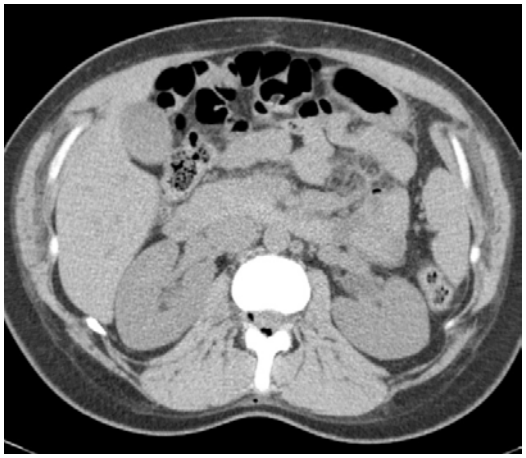


Figure 2. Axial non-contrast CT shows extradural intra-spinal air at one level. Subcutaneous focus of air is visualized in tract from the epidural injection.

Discussion

Pneumorrhachis is defined by the presence of air inside the spinal canal.[1] It is a rare radiological finding because it is typically asymptomatic and resolves itself. Therefore, it is usually discovered accidentally. PR can be caused by various non-traumatic, traumatic, and iatrogenic etiologies. The most common cause of PR is iatrogenic, typically through epidural injection because lightly pressurized air is used to find the epidural space. However, because iatrogenic PR is typically asymptomatic and spontaneously resolved, it is often difficult to detect, making this case more interesting. PR can be symptomatic in rare cases as a result of changes in intra-spinal pressure.

Pneumorrhachis generally is demonstrated best on computed tomography (CT) scanning, but magnetic resonance imaging or cervical plain radiography also may be used.[1] Typically, air either enters the epidural space or continues deeper into the subarachnoid space.[2] Because the specific location of the pneumorrhachis determines its clinical consequences, it is important to distinguish between the presence of air in the epidural or subarachnoid space.[2] Even with CT scanning, the difference may be difficult to distinguish. PR in the epidural space is typical and complete reabsorption occurs spontaneously. However, subarachnoid PR is more likely to be symptomatic. Subarachnoid PR often is caused by trauma or extensive surgical exposure of the spinal nerve root.[3]

Typically not a primary clinical diagnosis, PR is underdiagnosed and coincident with underlying injuries and diseases. It is common that PR is found in association with air distribution in other body cavities, such as pneumothorax, pneumomediastinum, or pneumopericardium.[4] Symptomatic PR can be associated with various symptoms due to changes in intra-spinal pressure, such as radicular pain and serious neurologic deficits. Because it typically is associated with traumas, PR is thought to increase morbidity and mortality.[5]

Epidural pneumorrhachis is typically asymptomatic. The intra-spinal air often is reabsorbed into the surrounding tissues. In some circumstances, subarachnoid PR intra-spinal air is not reabsorbed spontaneously and can be symptomatic. Due to the rarity of symptomatic PR, there are no standard guidelines for the treatment and management of PR. Treatment is often multidisciplinary because all contributing factors of PR must be addressed. Some possible treatments for PR are intravenous dexamethasone, air aspiration to decompress the epidural space, along with large doses of inspired oxygen to encourage the reabsorption of air from the subdural space.[6]

References

[1] Oertel MF, Korinth MC, Reinges MH, Krings T, Terbeck S, Gilsbach JM. Pathogenesis, diagnosis and management of pneumorrhachis. Eur Spine J 2006; 15(Suppl 17):636-643. PMID: 16835735.

[2] Place JN, Pezzuti RT. Clinical significance of traumatic pneumorrhachis. AJR Am J Roentgenol 1989; 153(3):655. PMID: 2763966.

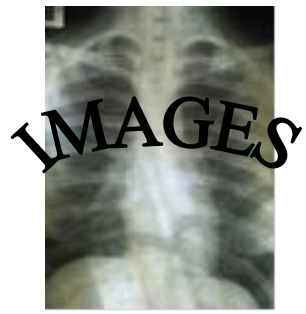
[3] Bilsky MH, Downey RJ, Kaplitt MG, Elowitz EH, Rusch VW. Tension pneumocephalus resulting from iatrogenic subarachnoid-pleural fistulae: Report of three cases. Ann Thorac Surg 2001; 71(2): 455-457. PMID: 11235688.

[4] Drevelengas A, Kalaitzoglou I, Petridis A. Pneumorrhachis associated with spontaneous pneumomediastinum. Eur J Radiol 1994; 18(2):122-123. PMID: 8055982.

[5] Kapur A, Sandhu S. Epidural pneumatosis: Not necessarily benign. AJNR Am J Neuroradiol 1994; 15(1):195-196. PMID: 8141057.

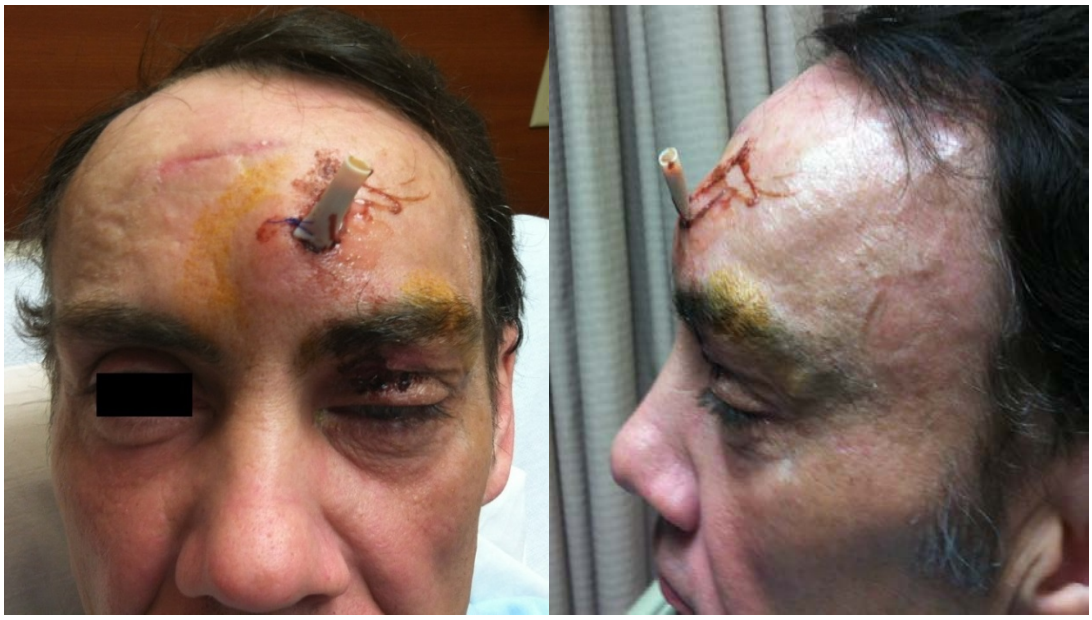
[6] Oertel MF, Korinth MC, Reinges HT, Krings T, Terbeck S, Gilsbach JM. Pathogenesis, diagnosis and management of pneumorrhachis. Eur Spine J 2006; 15(Suppl 5):636-643.

Keywords: pneumorrhachis, epidural injections, iatrogenic disease, anesthesia, radiology

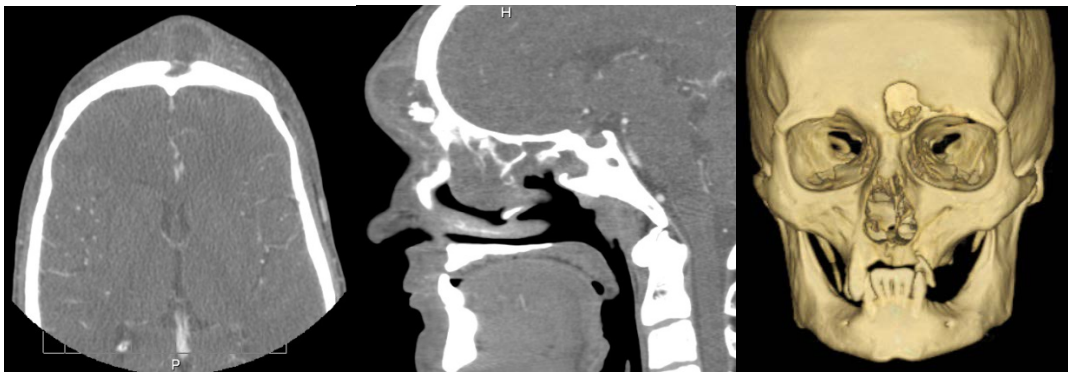


Pott's Puffy Tumor after Head Trauma

Carla Chalouhy, M.D.[1], Elie Chalhoub, M.D.[2], Joseph Meouchy, M.D.[3], Thomas A. Moore, M.D.[4]
[1]University of Balamand School of Medicine, Deir El-Balamand, Al-Kurah, Lebanon
[2]Tulane University School of Medicine, New Orleans, LA
[3]University of Southern California Keck School of Medicine, Los Angeles, CA
[4]University of Kansas School of Medicine-Wichita Center for Infectious Diseases, Wichita, KS



A previously healthy 43-year-old male presented two weeks after head trauma. He complained of worsening headache with swelling of the forehead and the left periorbital area, purulent discharge from the left eye, and rhinorrhea that began a few days prior to presentation. CT of the head and maxillofacial bones are shown below. He underwent incision and drainage of his abscesses. Operative cultures grew streptococcus intermedius and coagulase-negative staphylococcus. He was sent home on a six-week course of oral clindamycin and intravenous ceftriaxone, based on sensitivities.



Discussion

Pott's puffy tumor was first described by Pott in 1760.[1] It is due to osteomyelitis of the frontal bone with subperiosteal abscess formation. The prevalence is unknown, but it is more common in adolescents and often associated with chronic sinusitis or trauma.[2] It is rare, especially in the antibiotic era. The risk of intracranial complications is high and includes meningitis, epidural or subdural empyema, brain abscess, and cavernous sinus thrombosis. Treatment is usually with long term antibiotics and surgical drainage.

References

[1] Pott P. Observations on the Nature of Consequences of Wounds and Contusions of the Head, Fractures of the Skull, Concussions of the Brain. London, UK: Hitch & Lowes, 1760.

[2] Forgie SE, Marrie TJ. Pott's puffy tumor. Am J Med 2008; 121(12):1041-1042. PMID: 19028195.

Keywords: Pott Puffy Tumor, craniocerebral trauma, osteomyelitis, case report