A Survey of Practitioner's Knowledge of Psychiatric Medication Costs

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Abstract

Introduction. Escalating medical costs continue to be an issue facing contemporary medicine. One factor contributing to this escalation may be physicians' knowledge of medication costs. As physicians increasingly face opportunities to treat a variety of symptoms and conditions in a single patient, including co-morbid psychiatric disorders or complications, accurate knowledge of medication costs becomes increasingly important.

Methods. Resident and attending physicians (N = 16) across the disciplines of internal medicine, psychiatry, and combined internal medicine/psychiatry from a large, mid-western medical school were surveyed on the costs of several medications that are used to manage physical and psychiatric symptoms.

Results. Differences were found in the perceived estimated cost of medications among practitioners particularly with specialty internal medicine training as compared to those with additional psychiatric training/experience. Trends also were noted across practitioners with psychiatric and internal medicine/psychiatry training.

Conclusions. The breadth of training and experience can affect accuracy in estimating anticipated costs of medication regimens.

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Introduction

The major factors contributing to high and rapidly growing health care costs remain an important issue facing the modern practice of medicine.[1] Some factors contribute to the high level of spending, others drive growth, and some play a role in both. Provider knowledge of various treatments is paramount in curbing these expenses.

Physicians have inadequate knowledge of medication costs.[2] Furthermore, medical schools generally do not teach costs of treatments to students. This information is learned most often during practice contributing to rising medical treatment expenditures.[3] With healthcare costs climbing, physicians should have an understanding about the general costs of the medications that they prescribe. To implement cost-saving changes, the deficiency must be recognized.[4]

Until recently, most schools included little information on financial factors in medical education, such as insurance coverage and how treatment costs affect patients' behavior. Once recognized, schools can have a positive impact on prescribing patterns by providing information regarding commonly used prescriptions. Okie[5] reported an interactive teaching conference with distribution of a pocket guide listing the average wholesale prices of over 100

medications commonly used in primary care. Appropriately, this intervention was associated with some change in prescribing habits. Without such interventions and insights, physicians may practice with little sense of how to make the most cost-effective choices for patients.[1]

Given the scope of issues treated and patients served, some physicians may be more inclined to appreciate financial aspects of recommended care provided they are educated on the general costs of medications being prescribed. Internists and psychiatrists may be susceptible to making errors in the estimation of medication costs despite ample opportunity to manage a variety of issues (psychiatric or otherwise).[6]

In the light of the ever-growing role of psychiatrists in general medical care (e.g., consultation services) and areas of combined specialization (e.g., dual training in internal medicine and psychiatry), further assessment regarding the knowledge of medication costs has an incrementally important role in psychiatry. Given these factors, the present study examined this knowledge of psychiatric medication costs by practitioners and residents from the areas of internal medicine, psychiatry, and combined internal medicine/psychiatry.

Methods

This study was approved by the Institutional Review Board at the University of Kansas Medical Center.

Participants. Sixteen anonymous respondents were comprised from a sample of 1) psychiatry residents, 2) attending psychiatrists, 3) internal medicine residents, 4) attending internists, 5) residents in internal medicine/psychiatry, and 6) attending physicians with board eligibility/certification in internal medicine and psychiatry. Residents were at various years of training across programs. Attending physicians varied in age and level of experience.

Procedures. The participants were given a 17-question survey administered through SurveyMonkey® (an internet survey website). The questionnaire was divided into six groups as defined in the subject selection section. The responses for each group were compiled collectively and compared to the true cost of medications, as referenced from national pharmacies. Participants completed the survey over a two-week period (6 psychiatry residents, 1 attending psychiatrist, 2 attending physicians with board eligibility/certification in internal medicine and psychiatry, 2 internal medicine/psychiatry residents, 3 internal medicine residents, and 2 attending internists).

The survey assessed estimated cost of a variety of commonly-used psychiatric medications including: tricyclic anti-depressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and atypical antipsychotics at varying doses (Lexapro®, Abilify®, Welbutrin®, Celexa®, Cymbalta®, Effexor®, Prozac®, Remeron®, Pamelor®, Tofranil®, Paxil®, and Xanax®). All medications were referred to as "generic" to blind expectations concerning medication costs. Dosages ranged from "5 mg" to "75 mg" under the prescribed duration of "a month" when participants were asked to anticipate prescription costs. Perceived costs were compared against actual costs averaged from six local pharmacies.

Data analysis. Data were averaged and compiled to examine potential group differences in perception of psychiatric medication costs.

Results

Average group differences were reviewed to estimate perception of medication costs. The perceived cost of Tofranil® among individuals with internal

medicine training suggested a higher perceived cost of this medication in clinical practice relative to practitioners in psychiatry. Practitioners with internal medicine training estimated Paxil® and Celexa® to be relatively more expensive compared to practitioners with psychiatry training. Abilify® was estimated to be less expensive in this group compared to psychiatry practitioners who estimated this medication to be more costly. These effects are described in Figure 1. Providers with combined training (e.g., internal medicine and psychiatry) tended to be more accurate in estimating psychiatric medication costs than physicians with primarily internal medicine training.

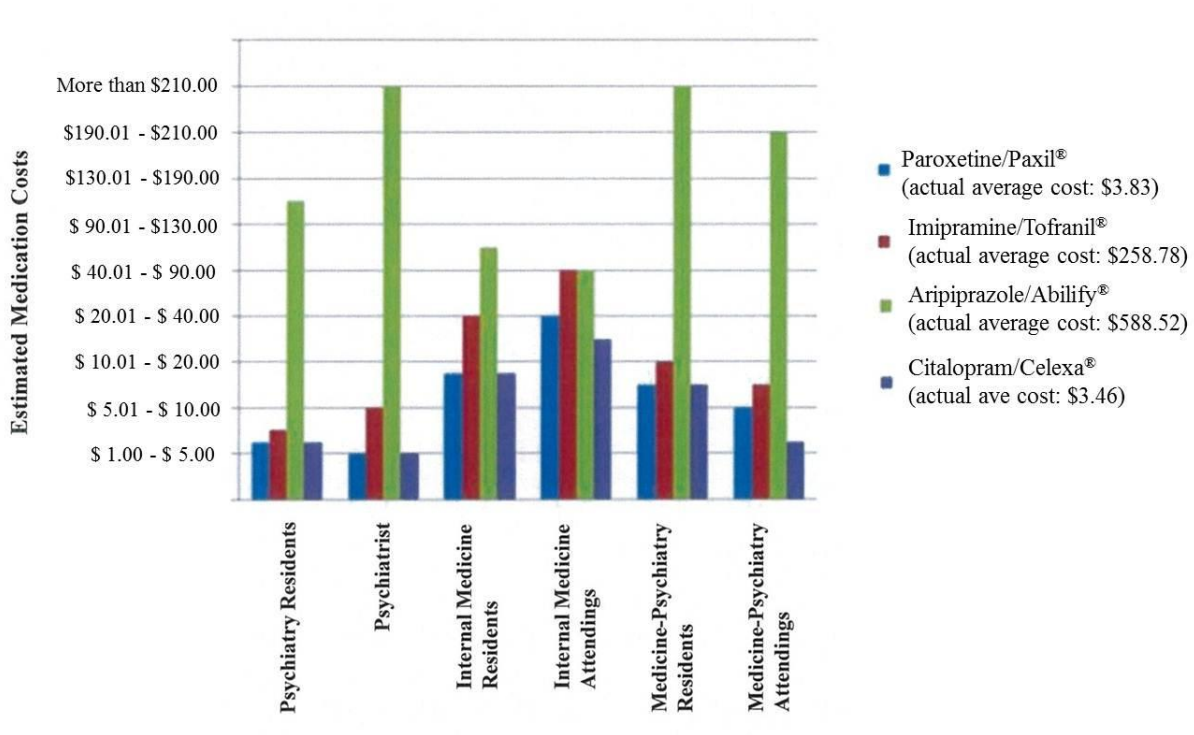

Figure 1. Summary of estimated medication costs across disciplines.

Discussion

Although the study sample is small, the resultant data suggested that differences exist in perception of medication costs that vary with relation to medical training and expertise. Examination of results suggested differences among groups of practitioners (psychiatry, internal medicine, and combined internal medicine/psychiatry) across a range of training levels. This was driven by a tendency for Tofranil® (a TCA primarily used for depression and chronic pain) to be rated as more expensive among physicians with only internal medicine training relative to physicians with training in psychiatry or combined internal medicine/psychiatry training. Additionally, trends were appreciable for Paxil®, Celexa®, and Abilify® across providers, suggesting that physicians with internal medicine view Paxil® and Celexa® as expensive, while viewing Abilify® as inexpensive relative to their colleagues in psychiatry. In noting these differences in estimated medication costs across providers, our findings were consistent with previous studies.

Hoffman et al.[1] examined physicians' and pharmacists' knowledge of non-steroidal anti-inflammatory drugs

(NSAIDs). They reported that although physicians overwhelmingly viewed cost as an important factor in prescribing medication (81% of respondents), only 75% of physicians correctly estimated the price of half of the medications surveyed; 65% of medication costs were underestimated. In this light, Hoffman and colleagues[1] concluded that practitioners could benefit from further knowledge to improve accuracy and avoid under-estimation of medication costs.

Our work extended this study, as prior research has not targeted the costs of psychiatric medications. In this study, over- and under-estimation of psychiatric medication costs occurred in particular among non-psychiatry specialists. Additionally, providers with combined training tended to be slightly more accurate across the medications surveyed.

There are many possible causes for the differences in provider response. One primary reason may be familiarity with these medications. Physicians with training in both internal medicine and psychiatry may have greater opportunity to learn about medications that can have applications across disciplines (e.g., managing pain, depression, and aiding sleep) due to the clinical issues that are faced. Greater exposure to medication costs can affect prescription patterns.

Recently, Cooke[4] commented that when providers are made aware of such issues, they are quick to learn and respond to the costs of medications. Similar observations have been noted across clinical and training settings.[5] These observations demonstrate that physicians can benefit from this type of education at any level of training. However, given a relative lack of education on medication costs provided in medical schools,[3] alongside the responsiveness physicians have to such education,[4-5] increasing this insight in a wide range of medical environments may be beneficial.

Increased training should yield cost reductions in healthcare by preventing underestimation of medication costs in the first place.[1] If providers have greater exposure and knowledge of medication costs, they will be in a better position to consider treatment costs when caring for a diverse patient population. Given the increasing treatment of psychiatric issues in general medicine, educating students and practitioners on psychiatric medical costs will become more important.

Another consideration is the increasing access to information concerning medication. The present survey was administered with no constraints in regards to use of standard references. As society modernizes and access to information is increasingly more available, a majority of practitioners and residents could access programs, reliably and easily, that give drug information via a variety of handheld devices, applications, and computer programs. In many cases, manufacturing/ pricing information can be provided for each medication which is generally accurate and used frequently by residents and medical providers as a cost reference while prescribing. It is unclear if any of our participants utilized this information while completing the survey.

Medical schools, residency programs, attending physicians, and private practitioners should seek up-to-date information concerning medicine costs in the best interest of patient care and potential reduction of in healthcare costs.

References

[1] Hoffman J, Barefield FA, Ramamurthy S. A survey of physician knowledge of drug costs. J Pain Symptom Manage 1995; 10(6):432-435. PMID: 7561225.

[2] Korn HM, Reichert S, Simon T, Halm EA. Improving physicians' knowledge of the costs of common medications and willingness to consider costs when prescribing. J Gen Intern Med 2003; 18(1):31-37. PMID: 12534761.

[3] Doebbeling CC, Pitkin AK, Malis R, Yates WR. Combined internal medicine-psychiatry and family medicine-psychiatry training programs, 1999-2000: Program directors' perspectives. Acad Med 2001; 76(12):1247-1252. PMID: 11739052.

[4] Cooke M. Cost consciousness in patient care - What is medical education's responsibility? N Engl J Med 2010; 362(14):1253-1255. PMID: 20357275.

[5] Okie S. Teaching physicians the price of care. The New York Times. 2010. Accessed at: http://www.nytimes.com/2010/05/04/health/04cost.html?pagewanted=all.

[6] Raynes NV. Involving residents in quality specification. Ageing Soc 1988; 18(1):65-78.

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Autoimmune Hemolytic Anemia with Myelodysplastic Syndrome

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Introduction

The myelodysplastic syndromes (MDS) are a heterogeneous group of clonal cell disorders characterized by ineffective hematopoiesis manifested by one or more cytopenias.[1] The incidence is higher in men, and is about 3-4 individuals per 100,000 in the United States and may exceed 20/ 100,000 persons after the age of 70 years.[2] Risk factors for development of MDS include prior chemotherapy, radiation therapy, smoking, and exposure to benzene. The most common cytogenetic alteration in MDS is a deletion of the short arm of chromosome 5. We report a patient with an isolated trisomy 21, which constitutes about 1.1-2.2 % of the total cytogenetic alterations in MDS.[3,4] To our knowledge, this is the first reported case of autoimmune hemolytic anemia (AIHA) and MDS with isolated trisomy 21.

Case Report

A 62-year-old Caucasian male was initially admitted for generalized weakness and fatigue. The symptoms started three months prior to presentation at the referring hospital. The patient reported anorexia, weight loss, and exercise intolerance. He denied any bleeding symptoms to suggest infection. On admission to our hospital, his vital signs were within normal limits. His physical exam showed pallor, but otherwise was unremarkable.

Initial labs are summarized in Table 1. His peripheral smear showed 65% neutrophils, 9% bands, 9% blasts, 2% metamyelocytes, and 1% myelocytes. He underwent a bone marrow biopsy, which was consistent with myelodysplastic syndrome (RAEB-1). His cytogenetics showed trisomy 21 as the sole abnormality. Testing for vitamin B_{12} and folic acid were unremarkable. The patient was diagnosed with AIHA and treatment was started with prednisone at 1 mg/kg.

The patient's hemoglobin improved with prednisone. The prednisone was tapered over two months and his Coombs testing became negative shortly after the course. The patient's platelet count continued to deteriorate and treatment was initiated with the hypomethylating agent, decitabine. The patient tolerated this treatment well and had improvement in his cytopenia. His course was complicated by gastrointestinal bleeding and a pneumonic infection. The patient died from complications of an empyema.

Discussion

This case illustrates a commonly overlooked association between two different hematologic diseases, myelo-dysplastic syndrome and autoimmune hemolytic anemia. Our patient had evidence of intravascular hemolysis, manifested by his reticulocytosis, high LDH and bilirubin,

Table 1. Initial labs obtained on admission.

Lab	Hb (g/dL)	WBC ($\times 10^9$/L)	Platelets ($\times 10^9$/L)	MCV (mm^3)	Reticulocyte count
Values	10.5	24.2	37	99	9.3%

Lab	LDH (IU/L)	Haptoglobin (mg/dL)	Bilirubin (mg/dL)	Coombs test
Values	568	3	2.8	Positive

and low haptoglobin. There was evidence of autoimmunity with the Coombs test positive for pan agglutinating IgG. This improved with standard first line treatment. The bone marrow biopsy result was consistent with myelodysplastic syndrome, refractory anemia with excess blasts (RAEB-1 with 7% blasts in the bone marrow).

Autoimmune hemolytic anemia is due to the immunologic destruction of red blood cells mediated by autoantibodies directed against red blood cells antigens.[5] The antibodies can be of "warm" or "cold" subtype. The majority of warm agglutinins are IgG subclass antibodies. They react to antigens at body temperature in contrast to cold agglutinins which are mostly IgM subclass, and react to RBC antigens at a temperature lower than the body's core temperature. The diagnosis usually is made with the finding of an elevated reticulocyte count, increased lactate dehydrogenase, and indirect bilirubin in the setting of a positive direct Coombs test (direct antiglobulin test).

There is increasing evidence that autoimmunity plays an important role in myelodysplastic syndromes. Autoimmune manifestations (AIM) are more common than thought in the setting of MDS. Their frequency ranges from 10-18.5% of patients with MDS.[6,7] These manifestations can be classified into five classes:[4]

1) Acute systemic vasculitis or autoimmune disorder.
2) Chronic or isolated autoimmune phenomena.
3) Classical connective tissue disorders.
4) Immune-mediated hematological abnormalities.
5) Asymptomatic serological immunologic abnormalities.

The association of AIM and MDS was first described in 1982 as AIHA one year after the diagnosis of MDS.[6] Subsequently, multiple cases and studies have been published emphasizing the relationship between autoimmunity and MDS.

In a study by Sokol et al.,[8] 15 of 46 patients with MDS had clinically important autoimmune hemolysis. Pendry et al.[9] reported a case of MDS presenting as AIHA. The first pediatric case was reported by Ören et al.[10] The improvement of both disorders was noticed with mycophenolate mofetil.[11] João et al.[12] and Terpos et al.[13] described two cases of MDS, AIHA, and non-Hodgkin's lymphoma. Giagounidis et al.[14] reported a case of AIHA and a case of autoimmune arthritis in association with MDS with 5q deletion. Pilorge et al.[15] reported three cases of AIM and MDS with improvement with 5-azacitidine.

The pathogenesis of the association of these two disorders is still unclear. Current hypotheses relate development of autoimmune hemolytic anemia to dysregulated immunity. In a study by Barcellini et al.,[16] 53.8% of patients showed autoimmune

phenomena to erythroblasts in the bone marrow, but none in the peripheral blood.[14,16]

AIHA in MDS may be underdiagnosed for several reasons including the assumption that anemia is due to MDS.[14] Besides, Coombs-negative hemolytic anemia can be masked by reticulocytopenia caused by MDS.

It is unclear if autoimmune manifestations carry any prognostic implications to the diagnosis of MDS. In a study by Enright et al.,[17] patients with the combination of the two disorders were younger, more often had MDS related to prior chemotherapy, and had additional cytogenetic abnormalities. The onset of AIM was associated with clinical deterioration, as the median survival after AIM diagnosis was only nine months compared to 25 months after MDS diagnosis. In addition, the initial response to steroids carried a better prognosis.

Conclusion

Autoimmune hemolytic anemia is a rare, but commonly overlooked cause of anemia in patients with myelodysplastic syndrome. Further reports may delineate the association of autoimmune manifestations and MDS better and its potential prognostic and therapeutic implications. A link may be found between chromosomal abnormalities and their concomitant incidence.

References

1 Barzi A, Sekeres MA. Myelodysplastic syndromes: A practical approach to diagnosis and treatment. Cleve Clin J Med 2010; 77(1):37-44. PMID: 20048026.

2 Rollison DE, Howlader N, Smith MT, et al. Epidemiology of myelodysplastic syndromes and chronic myeloproliferative disorders in the United States, 2001-2004, using data from the NAACCR and SEER programs. Blood 2008; 112(1):45-52. PMID: 18443215.

3 Haase D. Cytogenetic features in myelodysplastic syndromes. Ann Hematol 2008; 87(7):515-526. PMID: 18414863.

4 Haase D, Germing U, Schanz J, et al. New insights into the prognostic impact of the karyotype in MDS and correlation with subtypes: Evidence from a core dataset of 2124 patients. Blood 2007; 110(13):4385-4395. PMID: 17726160.

5 Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J. Harrison's Principles of Internal Medicine. 18th edition. New York: McGraw-Hill, 2012. ISBN: 007174889X.

6 Saif MW, Hopkins JL, Gore SD. Autoimmune phenomena in patients with myelodysplastic syndromes and chronic myelomonocytic leukemia. Leuk Lymphoma 2002; 43(11):2083-2092. PMID: 12533032.

7 Giannouli S,Voulgarelis M, Zintzaras E, Tzioufas AG, Moutsopoulos HM. Autoimmune phenomena in myelodysplastic syndromes: A 4-yr prospective study. Rheumatology (Oxford) 2004; 43(5):626-632. PMID: 14983106.

8 Sokol RJ, Hewitt S, Booker DJ. Erythrocyte autoantibodies, autoimmune haemolysis, and myelodysplastic syndromes. J Clin Pathol 1989; 42(10): 1088-1091. PMID: 2584409.

9 Pendry K, Harrison C, Geary CG. Myelodysplasia presenting as autoimmune haemolytic anaemia. Br J Haematol 1991; 79(1):133-134. PMID: 1654992.

10 Oren H, Ucar C, Gülen H, Duman M, Irken G. Autoimmune hemolytic anemia occurring with myelodysplastic syndrome: Report of a pediatric case and review of the literature. Ann Hematol 2001; 80(9):540-542. PMID: 11669304.

11 Lin JT, Wang WS, Yen CC, et al. Myelodysplastic syndrome complicated by

autoimmune hemolytic anemia: Remission of refractory anemia following mycophenolate mofetil. Ann Hematol 2002; 81(12):723-726. PMID: 12483369.

[12] João M, Silva N, Lucas M, et al. Long lasting myelodysplastic syndrome complicated by autoimmune hemolytic anemia and non-Hodgkin's lymphoma. Eur J Haematol 2002; 68(2):122-124. PMID: 11982620.

[13] Terpos E, Theocharis S, Panitsas F, Philippidis T, Kotronis E, Karkantaris C. Autoimmune hemolytic anemia with myelodysplastic features followed by bilateral adrenal non-hodgkin lymphoma: A case report and review of the literature. Leuk Lymphoma 2004; 45(11):2333-2338. PMID: 15512826.

[14] Giagounidis AA, Haase S, Germing U, Heinsch M, Aul C. Autoimmune disorders in two patients with myelodysplastic syndrome and 5q deletion. Acta Haematol 2005; 113(2):146-149. PMID: 15802895.

[15] Pilorge S, Doleris LM, Dreyfus F, Park S. The autoimmune manifestations associated with myelodysplastic syndrome respond to 5-azacytidine: A report on three cases. Br J Haematol 2011; 153(5): 664-665. PMID: 21275970.

[16] Barcellini W, Zaninoni A, Imperiali FG, et al. Anti-erythroblast autoimmunity in early myelodysplastic syndromes. Haematologica 2007; 92(1):19-26. PMID: 17229631.

[17] Enright H, Jacob HS, Vercellotti G, Howe R, Belzer M, Miller W. Paraneoplastic autoimmune phenomena in patients with myelodysplastic syndromes: Response to immunosuppressive therapy. Br J Haematol 1995; 91(2):403-408. PMID: 8547082.

Keywords: autoimmune hemolytic anemia, myelodysplastic syndromes, case report

Hydroxychloroquine Associated Hyperinsulinemic Hypoglycemia

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Introduction

Hypoglycemia in the patient without diabetes mellitus is uncommon.[1] An initial evaluation of hypoglycemia begins with confirming Whipple's triad which includes: the presence of sympathoadrenal and neuroglycopenic symptoms, documented low plasma glucose concentration, and resolution of symptoms when plasma glucose is raised.[2] Hypoglycemia secondary to hydroxychloroquine previously has been documented in humans.[3,4] We describe a case of severe hyperinsulinemic hypoglycemia in a patient initiated on hydroxychloroquine therapy.

Case Report

A 66-year-old female with a complex medical history including rheumatoid arthritis and pyoderma gangrenosum, but without known history of either diabetes mellitus or exposure to glucose lowering medications, was admitted to the hospital for evaluation and management of anasarca. While hospitalized, the patient was initiated on hydroxychloroquine for management of her rheumatologic disorders. Within hours of her first dose of hydroxychloroquine, the patient developed hypoglycemia with a glucose value of 28 mg/dL on serum measurement. She was symptomatic with diaphoresis, tremors, and confusion. Her symptoms resolved with administration of dextrose.

Additional pertinent medical history included a long-standing history of chronic exogenous steroid use due to her rheumatologic disorders. At the time of this hypoglycemic event, the patient was placed on stress dose steroids (hydrocortisone 100mg IV q 8 hours). She did not have a history of prior bariatric surgery, renal insufficiency, uncontrolled hypothyroidism, or findings to suggest an infectious etiology of hypoglycemia.

Although standard hypoglycemic laboratory was not obtained with the initial hypoglycemic event, the patient had multiple additional episodes of symptomatic hypoglycemia, despite receiving stress dose steroids, at which time a standard hypoglycemic laboratory evaluation was undertaken. Diagnostic laboratory captured at the time of a recurrent hypoglycemic event was consistent with hyperinsulinemic hypoglycemia (Table 1).

In light of hyperinsulinemic hypoglycemia without known exposure to oral hypoglycemic agents, a computed tomography scan of the abdomen was obtained. This study was negative for any evident pancreatic mass and given the temporal relationship of administration of hydroxychloroquine to development of hypoglycemia, no further imaging was obtained. Due to prior case reports associating hydroxychloroquine with hypoglycemia,

Table 1. Hypoglycemic laboratory evaluation.

	Glucose	Insulin	C-peptide	Proinsulin	Hypoglycemic Screen
Reference Ranges for Endogenous Hyperinsulinemia	< 55 mg/dL	≥ 3.0 U/mL	≥ 0.2 nmol/L	≥ 5 pmol/L	Negative
Patient Values	53 mg/dL	102.9 U/mL	6.0 nmol/L	330 pmol/L	Negative

this medication was discontinued prior to any additional doses being administered. Hypoglycemia persistently recurred over an approximately ten-hour period following the first dose of hydroxychloroquine, then it resolved without recurrence, confirming hydroxychloroquine as the causative agent. The patient was followed in the hospital setting for an additional four days without recurrence of hypoglycemia. In addition, she was seen in ambulatory follow-up within one month of discharge without recurrent events.

Discussion

Hypoglycemia is a rare, but well recognized, adverse effect of treatment with anti-malarial agents including hydroxychloroquine and chloroquine.[3] Hypoglycemia secondary to hydroxychloroquine has been documented previously in the medical literature, both in patients with diabetes on stable doses of glucose lowering drugs as well as patients without a prior history of diabetes and on no hypoglycemic agents.[3,6]

The mechanism of hydroxychloroquine-induced hyperinsulinemic hypoglycemia has been inferred from studies on chloroquine, which is structurally similar. In the streptozocin-treated type 1 diabetic rat model, chloroquine led to higher levels of insulin with concomitant drops in blood glucose.[9] Additionally, a second study has shown an increase in the level of plasma immunoreactive insulin in rats treated with chloroquine.[10] This is thought to be due to enhanced insulin secretion from beta cells,[10] as well as inhibition of insulin degradation by chloroquine.[11]

Animal studies have shown that hydroxychloroquine increases insulin levels in diabetic rats, thereby decreasing serum glucose levels. This increase in insulin also has been found to be concentration-dependent to the amount of hydroxychloroquine administered.[12]

The glycemic effects of hydroxychloroquine in humans have been well-described in several clinical studies evaluating its use in treatment and prevention of diabetes mellitus. It improves glycemic control in individuals with diabetes with and without autoimmune diseases.[13,14] It significantly decreased glycated hemoglobin and fasting glucose in patients with type 2 diabetes mellitus that previously had been non-responsive to sulfonylureas and other medications for diabetes.[13-15] Hydroxychloroquine has been associated with a decreased risk of development of diabetes mellitus in patients with rheumatologic disorders.[16-18]

Conclusion

We described a case of severe and persistent hyperinsulinemic hypoglycemia with initiation of hydroxychloroquine in a patient without diabetes mellitus. This case report adds to the sparse literature surrounding this important clinical topic. Based on animal data, the cause of hydroxychloroquine-induced hyperinsulinemic hypoglycemia is thought to occur via

two different mechanisms: enhanced insulin secretion from beta cells as well as inhibition of insulin degradation. The proposed mechanisms behind hydroxychloroquine-induced hypoglycemia are consistent with the laboratory results of our patient. Although the literature supporting the role of hydroxychloroquine as an agent associated with hyperinsulinemic hypoglycemia is limited, there is mounting evidence of hydroxychloroquine's role in diabetes prevention in patients' with rheumatologic disorders. Healthcare providers and patients should we aware of the potential for modulation of glycemic status with this class of medications.

References

[1] Nirantharakumar K, Marshall T, Hodson J, et al. Hypoglycemia in non-diabetic in-patients: clinical or criminal? PLoS One 2012; 7(7):e40384**.** PMID:22768352.

[1] Cryer PE, Axelrod L, Grossman AB, et al. Evaluation and management of adult hypoglycemic disorders: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2009; 94(3):709-728. PMID: 19088155.

[2] Shojania K, Koehler BE, Elliott T. Hypoglycemia induced by hydroxychloroquine in a type II diabetic treated for polyarthritis. J Rheumatol 1999; 26(1): 195-196. PMID: 9918262.

[3] Powrie JK, Smith GD, Shoajee-Moraddie F, Sönksen PH, Jones RH. Mode of action of chloroquine in patients with non-insuline-dependent diabetes mellitus. Am J Physiol 1991; 260(6 Pt.1):E897-E904. PMID: 2058666.

[4] Cansu DU, Korkmaz C. Hypoglycaemia induced by hydroxychloroquine in a non-diabetic patient treated for RA. Rheumatology (Oxford) 2008; 47(3):378-379. PMID: 18222983.

[5] Kang L, Mikuls TR, O'Dell JR. Hydroxychloroquine: A diabetic drug in disguise? BMJ Case Rep 2009. Epub 2009 Mar 2. PMID: 21686697.

[6] Unübol M, Ayhan M, Guney E. Hypoglycemia induced by hydroxychloroquine in a patient treated for rheumatoid arthritis. J Clin Rheumatol 2011; 17(1):46-47. PMID: 21169846.

[7] Garcia-Webb P, Bonser AM. Insulin binding and degradation in isolated hepatocytes from streptozotocin injected rats. Biochem Biophys Res Commun 1985; 128(2):487-493. PMID: 3888217.

[8] Asamoah KA, Robb DA, Furman BL. Chronic chloroquine treatment enhances insulin release in rats. Diabetes Res Clin Pract 1990; 9(3):273-278. PMID: 2146103.

[9] Kobayashi M, Iwasaki M, Shigeta Y. Receptor mediated insulin degradation decreased by chloroquine in isolated rat adipocytes. J Biochem 1980; 88(1):39-44. PMID: 6997286.

[10] Emami J, Gerstein HC, Pasutto FM, Jamali F. Insulin-sparing effect of hydroxychloroquine in diabetic rats is concentration dependent. Can J Physiol Pharmacol 1999; 77(2):118-123. PMID: 10535702.

[11] Penn SK, Kao AH, Schott LL, et al. Hydroxychloroquine and glycemia in women with rheumatoid arthritis and systemic lupus erythematosus. J Rheumatol 2010; 37(6):1136-1142. PMID: 20436082.

[12] Quatraro A, Consoli G, Magno M, et al. Hydroxychloroquine in decompensated, treatment-refractory noninsulin-dependent diabetes mellitus. A new job for an old drug? Ann Intern Med 1990; 112(9):678-681. PMID: 2110430.

[13] Gerstein HC, Thorpe KE, Taylor DW, Haynes RB. The effectiveness of hydroxychloroquine in patients with type 2

diabetes mellitus who are refractory to sulfonylureas-a randomized trial. Diabetes Res Clin Pract 2002; 55(3):209-219. PMID: 11850097.

[14] Wasko MC, Hubert HB, Lingala VB, et al. Hydroxychloroquine and risk of diabetes in patients with rheumatoid arthritis. JAMA 2007; 298(2):187-193. PMID: 17622600.

[15] Solomon DH, Massarotti E, Garg R, Liu J, Canning C, Schneeweiss S. Association between disease-modifying antirheumatic drugs and diabetes risk in patients with rheumatoid arthritis and psoriasis. JAMA 2011; 305(24):2525-2531. PMID: 21693740.

[16] Bili A, Sartorius JA, Kirchner HL, et al. Hydroxychloroquine use and decreased risk of diabetes in rheumatoid arthritis patients. J Clin Rheumatol 2011; 17(3):115-120. PMID: 21441823.

Keywords: hydroxychloroquine, hyper-insulinemia, hypoglycemia

Can Aseptic Meningitis Present With Very High CSF Protein?

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Introduction

Cerebrospinal fluid (CSF) analysis commonly is performed to evaluate disease of the central nervous system (CNS). Protein concentration in the CSF varies with the type and degree of pathology in the CNS. Elevated CSF protein above 0.4 g/l and up to 4.5 g/l has been reported in viral and bacterial infections, intracranial hemorrhages, multiple sclerosis, Guillain Barre syndrome, malignancies, and inflammatory disease of the CNS.[1] On the other hand, very high levels above 4.5 g/l usually are seen only in suppurative bacterial meningitis and CNS malignancy.[1-3]

Aseptic meningitis refers to cases with the clinical picture of meningitis and a CSF analysis revealing slightly elevated white blood cell count, usually lymphocytes, a slightly elevated protein level, and normal to slightly decreased glucose level. The CSF in these cases is with absence of bacterial or fungal colonies. We report a case of a patient with the clinical picture for aseptic meningitis except for a CSF protein above 5 g/l. Clinicians should be aware that in rare situations very high CSF protein can be seen in self-limiting aseptic meningitis.

Case Report

A 26-year-old male presented to the emergency department complaining of a severe generalized and pounding headache that started suddenly. He also reported associated abdominal pain, nausea, and vomiting. On physical examination, his vital signs (blood pressure, pulse, and temperature) were normal. He was obtunded and had a depressed level of consciousness, but was arousable, responsive, oriented to time, person, and situation, withdrew to pain, and followed orders precisely. He had no focal motor deficits, no Babinski signs, and no limb ataxia. He had normal deep tendon reflexes. His cranial nerves were intact and his fundi were normal. His examination was pertinent for neck stiffness. Examination of the lungs, heart, and abdomen was normal. In view of these findings, the patient was suspected to be suffering from meningitis.

Routine CSF studies (cell count, protein, and sugar) are detailed in Table 1. CSF gram stain and culture for bacteria, mycobacterium, and fungal species were negative. Ziehl-Neelsen stain was negative. CSF cytology revealed numerous lymphocytes and macrophages, but no malignant cells. CSF PCR for human immunodeficiency virus (HIV 1 and 2), herpes simplex virus (HSV), varicella zoster virus (VZV), cytomegalovirus (CMV), and Epstein-Barr virus (EBV) were negative. No oligoclonal bands were detected.

Blood studies revealed an elevated white blood cell (WBC) count of 14,400 with lymphocyte predominance. His chemistry studies, including an amylase and lipase, were normal. His blood glucose was 98 mg/dl. Malaria smear was negative. Blood cultures did not grow any organism after five days of incubation. Carcino-embryonic

antigen (CEA) was 1.2 ng/ml and erythrocyte sedimentation rate (ESR) was 6 mm/hr. Urine analysis was normal. Other serum studies were performed and were negative or normal (Table 2).

Table 1. CSF results during the patient's hospitalization.

Date	Glucose (mg/dl) CSF / serum	Protein (g/l) CSF / serum	Cell count WBC/RBC	% Lymphocytes	% Monocytes
Day 1	25 / 96	4.45 / 36	3544 / 306	77	23
Day 2	39 / 102	5.15 / 44	2880 / 43	92	8
Day 8	41 / 104	2.03 / 39	350 / 30	80	20
Day 13	43 / 101	1.27 / 41	174 / 2	96	4

Table 2. Serum tests performed and the results.

Test	**Results**
Antinuclear antibodies (ANA)	Negative
Anti-neutrophil cytoplasmic antibodies	Negative
Angiotension converting enzyme (ACE)	Negative
Anti-cardiolipin antibodies	Negative
C3 &C4 complement levels	Normal
HIV 1 &2 antibodies	Negative
Cryptococcus	Nonreactive
VDRL	Nonreactive
Brucella	Normal
Salmonella	Normal
Trypanosoma-brucei antibodies	Normal
Trypanosoma-cruzi antibodies	Normal
Flavivirus	Normal
West Nile virus	Normal

Magnetic resonance imaging of the brain revealed leptomeningeal enhancement, but no evidence for pachymeningitis. Computed tomography of the chest, abdomen, and pelvis was normal.

The patient remained in the hospital for two weeks during which he gradually improved with decrease in the headache and lethargy and improvement in his level of consciousness and general well-being without any medical therapy.

Discussion

Cerebrospinal fluid analysis (CSF) analysis is an important step in the diagnosis of central nervous system diseases. An elevated CSF white blood cell count is seen in infectious and inflammatory conditions. A protein level which rises in infectious, inflammatory, demyelinating, and malignant conditions usually reflects the disease process, and it may be elevated falsely by the presence of red blood cells (RBC) in a hemorrhagic tap.[1] The latter can be corrected by subtracting 1 mg/dl (0.01 g/l) of protein for every 1000 RBC/mm^3.

A CSF protein level of 0.4 - 22.0 g/l has been reported in bacterial infections, 0.3 - 3.1 g/l in cryptococcal infections, and 0.2 - 11.4 g/l in tuberculosis meningitis.[1,3,4] The

CSF protein level in brain tumors, whether primary or metastatic, has been reported between 0.15- 19 g/l.[1,3] In leptomeningeal metastasis, the CSF protein is elevated in 80% of the cases with a median concentration of 1 g/l.[4] Brain abscesses may raise the CSF protein between 0.16 - 2.88 g/l.[1] In demyelinating CNS disease, the CSF protein level rises to 0.13 - 1.33 g/l.[1,3] Cerebral trauma and seizure disorder may raise the protein level to 0.1 – 2.0 g/l.

The blood-CSF barrier is a physical barrier consisting of different anatomical structures for the diffusion and filtration of molecules from the serum to the CSF. Elevated CSF protein can be either secondary to local synthesis of protein within the CNS, or impaired resorption of the CSF protein by the arachnoid villi, or increased entry of plasma proteins due to increased permeability of the blood brain barrier.[3] The comparison of the CSF to serum protein usually reflects the type of pathology.

A significant increase in CSF protein level is seen in bacterial meningitis in comparison to viral meningitis.[4] In viral or aseptic meningitis, the CSF glucose is normal or low, the protein level is normal to elevated, the WBC count is elevated, and bacterial cultures are negative. The level of protein in these cases is usually between 0.1 - 4.0 g/l.[1-3,5,6] In the majority of cases, no definite diagnosis is reached, and patients are labeled to have aseptic meningitis. No definite etiology usually is found in 75% of patients labeled to have aseptic meningitis.[7,8] There are no reports in the literature whereby the CSF protein was above 4 g/l in cases of aseptic meningitis.[9]

The interesting aspect of this case was that the patient had elevated CSF WBC count, significantly elevated CSF protein, and significantly low sugar, absent bacterial cultures and viral PCRs, and spontaneous normalization of these results with no treatment. This picture is suggestive of aseptic meningitis rather than infectious meningitis and alerts clinicians to accept these CSF findings in certain cases of aseptic meningitis. Clinicians in general and neurologists in particular should be aware that, in exceptional cases, aseptic meningitis could present with very high levels of CSF protein up to 5 g/l.

References

1 Seehusen DA, Reeves MM, Fomin DA. Cerebrospinal fluid analysis. Am Fam Physician 2003; 68(6):1103-1108. PMID: 14524396.

2 Carbonnelle E. [Laboratory diagnosis of bacterial meningitis: usefulness of various tests for the determination of the etiological agent]. [French] Med Mal Infect 2009; 39(7-8):581-605. PMID: 19398286.

3 Lee BE, Davies HD. Aseptic meningitis. Curr Opin Infect Dis 2007; 20(3):272-277. PMID: 17471037.

4 Deisenhammer F, Bartos A, Egg R, et al. Routine cerebrospinal fluid analysis. In: Hughes R, Brainin M, Gilhus NE. (Eds.) European Handbook of Neurological Management. 1st edition. Oxford, UK: Blackwell Publishing Ltd, 2008, pp. 14-27. ISBN: 1405130504.

5 Abro AH, Abdou AS, Ali H, Ustadi AH, Hassab AAH. Cerebrospinal fluid analysis acute bacterial vs viral meningitis. Pak J Med 2008; 24(5):645-650.

6 Jurado R, Walker HK. Cerebrospinal Fluid. In: Walker HK, Hall WD, Hurst JW. (Eds.) Clinical Methods: The History, Physical and Laboratory Examination. 3rd edition. Boston: Butterworths, 1990, pp. 371-382. ISBN: 0-409-90077-X.

7 O'Sullivan SS, O'Connell B, Redmond J. Aseptic meningitis: A 2-year review of

diagnoses reached in a tertiary neurological and infectious disease centre. Ir J Med Sci 2007; 176(3):215-219. PMID: 17659429.

[8] Hosoya M, Honzumi K, Sato M, Katayose M, Kato K, Suzuki H. Application of PCR for various neurotropic viruses on the diagnosis of viral meningitis. J Clin Virol 1998; 11(2):117-124. PMID: 9785213.

[9] Jurado R, Walker HK. Cerebrospinal Fluid. In: Walker HK, Hall WD, Hurst JW. (Eds.) Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd Edition. Boston: Butterworths, 1990. ISBN: 0-409-90077-X.

Keywords: aseptic meningitis, cerebrospinal fluid proteins, central nervous system diseases

Glycogenic Hepatopathy: A Complication of Type 1 Diabetes Mellitus

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Introduction

Glycogenic hepatopathy is an acquired glycogen storage disease seen in type 1 diabetes, particularly those that are not well controlled.[1-3] It causes elevated transaminase levels, hepatomegaly, and abdominal pain. It is less recognized than non-alcoholic steato-hepatitis (NASH) which occurs more commonly in type 2 diabetes with metabolic syndrome, but is an important diagnosis to consider in the appropriate clinical setting.

Case Report

A 25-year-old white female presented to the emergency department due to bilateral flank pain. The pain was present for two days and was progressing. It was stabbing in nature and did not radiate. The patient had associated nausea and vomiting. She also noted that the pain was similar to symptoms she had one month prior when she was treated for pyelonephritis.

The patient's past medical history was significant for uncontrolled type 1 diabetes mellitus diagnosed at age 12, hypo-thyroidism, and chronically elevated transaminase levels of undefined etiology. Additionally, she recently was treated with ceftriaxone and ciprofloxacin for pyelo-nephritis. Her medications included glargine insulin, insulins aspart, and levothyroxine. She reported smoking one-half pack of cigarettes per day, occasional marijuana use, and rare alcohol use. She had no knowledge of any family history of liver disease. Her review of symptoms was negative, notably for dysuria, fever, or chills.

The patient was afebrile with normal vital signs. Her physical exam was benign other than mild costovertebral angle tenderness bilaterally. Initial labs showed a normal complete blood count, electrolytes, and kidney function. Transaminase levels were abnormal with a serum aspartate aminotransferase (AST) level of 870 units/L (normal < 37), an alanine aminotransferase (ALT) level of 272 units/L (< 65), and an alkaline phosphatase level of 262 units/L (< 136). The international normalized ratio was 0.9, the bilirubin level was 0.2 mg/dL (0.2 - 1.2), and albumin concentration was 3.2 gm/dL (3.4 - 4.5). Urinalysis showed trace leukocyte esterase activity, 3+ glucose, and 1+ bacteria. A urine drug screen was negative and acetaminophen and alcohol were not detected in the serum. Hemoglobin A1c was 11.0%.

Computed tomography (CT) revealed an enlarged liver with attenuation measured at 82 Hounsfield units (HU; normal for the liver is 40 - 60; Figure 1). Based on imaging results, hemochromatosis, hemosiderosis, or other heavy metal deposition was considered. Comparison was made to a CT scan done eight years previously which had similar findings and recommendations.

Review of the patient's prior hospital-izations revealed elevated transaminase levels dating back 11 years. Serologies for

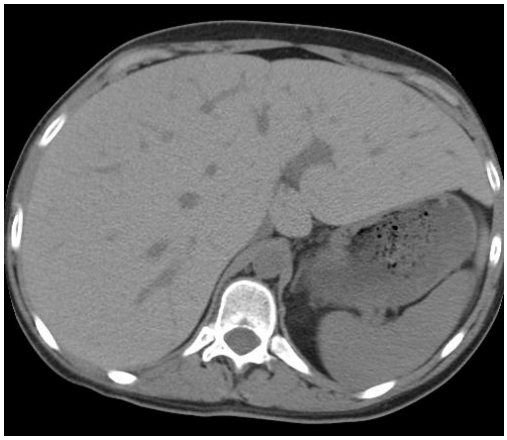

Figure 1. CT of the abdomen. The liver is enlarged and has increased attenuation at 82 Hounsfield units.

human immunodeficiency virus and viral hepatitis were negative over this time frame, but no other workup had been done. During the current hospitalization, the transaminase levels trended up over the first several days and a workup was initiated to determine the cause of the elevation with the following results: ferritin level, 78 ng/ml (normal 7 - 283), percent saturation, 17% (11 - 46), total iron binding capacity, 322 mcg/dl (250 - 450), alpha-1-antitrypsin level, 94 mg/dl (90 - 200), ceruloplasmin level 20.7 mg/dl, (16 - 45), and absence of anti-nuclear, anti-smooth muscle, tissue transglutaminase, and endomysial antibodies.

The patient's transaminase levels peaked on day four of hospitalization with an AST level of 2,386 units/L and ALT level of 784 units/L. This was the highest they had been at any point in the past. A liver biopsy (Figure 2) showed pale cytoplasm on H&E stain, no evidence of fibrosis on trichrome stain, markedly positive glycogen staining on a periodic acid-Schiff stain **(**PAS**),** and washout of the PAS stain after addition of diastase (an enzyme that digests pure glycogen). These findings were consistent with glycogenic hepatopathy.

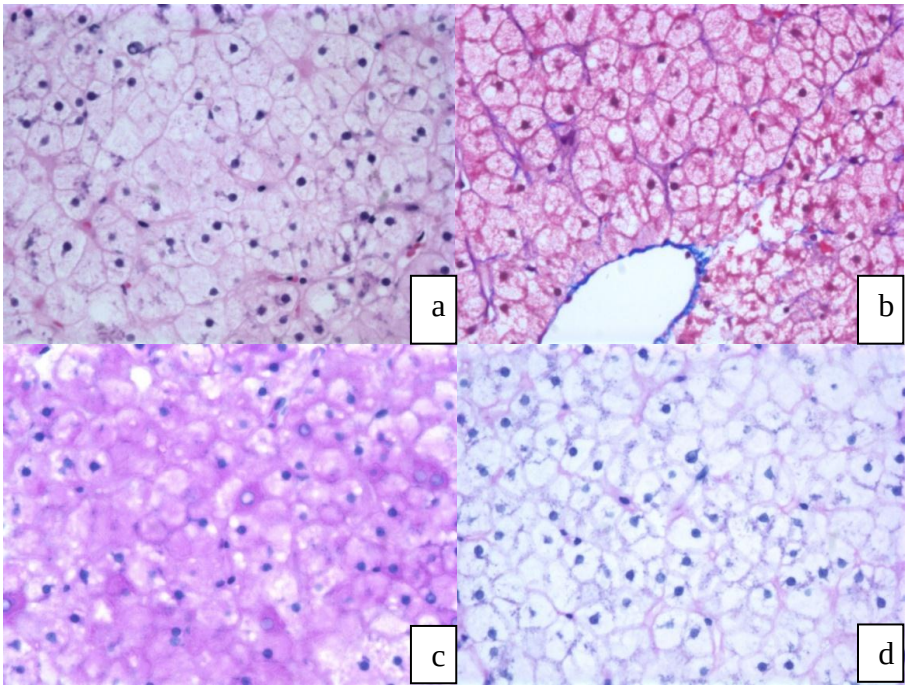

Figure 2. (a) H&E shows pale cytoplasm. (b) Trichrome shows no fibrosis. (c) PAS is positive for glycogen. (d) PAS washed out after diastase.

Pathophysiology

Glycogenic hepatopathy (GH) is characterized by abnormal glycogen accumulation in the liver. It is an acquired disease seen in type 1 diabetes, generally patients with poor glycemic control.[1-3] It originally was described by Mauriac in1930, after the discovery of insulin therapy for type 1 diabetes.[4] In children, it is a syndrome of hepatomegaly, growth impairment, and cushingoid features. In adults, it is seen as isolated liver disease without the other syndromic features.[3]

The classic presentation of GH is a triad of hepatomegaly, abdominal pain, and elevated serum transaminases, but not all of these features are required. CT scanning generally shows increased liver attenuation.[5] Definitive diagnosis is made by biopsy which shows glycogen accumulation within hepatocytes. Generally, fibrosis is minimal.

The glycogen accumulation seen in GH is dependent on high levels of both serum glucose and insulin at different times.[1,3] High serum glucose levels allow passive diffusion of glucose into hepatocytes where glucose is converted to glucose-1-phosphate by glucokinase and is trapped in the cell. Glucose-1-phosphate is converted to glycogen by glycogen synthase. Glycogen synthase is activated by dephosphorylation by glycogen synthase phosphatase. The concentration of this enzyme is maintained by insulin and its activity depends on glucose. In patients with poorly controlled type 1 diabetes who administer a large insulin bolus, hepatocytes will have a large amount of glucose-1-phosphate which will be converted to glycogen due to the activity of glycogen synthase. Glycogenic hepatopathy does not occur in all patients with poorly controlled type 1 diabetes. The development of GH is dependent on defects in regulatory proteins in susceptible patients (type 1 diabetes), which are clinically insignificant in the rest of the population.[3]

Treatment and Prognosis

Treatment of GH is limited to more rigorous blood glucose control. Tight management of glucose and insulin levels can lead to complete resolution of the clinical, laboratory, and histologic findings.[6-8] Glycogenic hepatopathy rarely progresses to fibrosis. In the largest case series investigating histology, 2 of 14 patients had only mild fibrosis, while the remaining 12 patients had none.[9] This contrasts with NASH which is seen more commonly in type 2 diabetes with metabolic syndrome and has a much higher rate of fibrosis and cirrhosis (37% of patients had cirrhosis in one study).[10]

Discussion

Some interesting aspects of GH are illustrated by this case. First, after admission, the transaminase levels trended up for the first four days. This may have been iatrogenic as she was given high doses of insulin to control her blood sugars. If true, it demonstrates the importance of high insulin levels for progression of this disease and may illustrate why GH was not described until after the discovery of insulin therapy. Additionally, this patient was known to have elevated transaminase levels for years, but on liver biopsy had no fibrosis, illustrating the typical lack of progression to fibrosis and cirrhosis in GH.

Our patient was informed that improvement in the control of her diabetes would reverse her liver disease. Three months after discharge, her hemoglobin A1c was 10.3%, down from 11.0% when she was hospitalized. Six months after discharge, her AST and ALT levels were 116 units/L and 87 units/L respectively, much lower than during her hospitalization.

Conclusion

Glycogenic hepatopathy is an acquired disorder of glycogen accumulation within

hepatocytes seen exclusively in persons with poorly controlled type 1 diabetes, typically presenting as elevated transaminase levels, hepatomegaly, and abdominal pain. In contrast to NASH, GH less commonly progresses to fibrosis and cirrhosis. Definitive diagnosis is made by liver biopsy, but an empiric trial of improved glucose control can be considered prior to biopsy in suspected cases. Treatment of GH is limited to improving glycemic control.

References

[1] Chatila R, West AB. Hepatomegaly and abnormal liver tests due to glycogenosis in adults with diabetes. Medicine (Baltimore) 1996; 75(6):327-333. PMID: 8982149.

[2] Rogal SS, Ukomadu C, Levy BD, Loscalzo J. Clinical problem-solving. A sweet source of abdominal pain. N Engl J Med 2011; 364(18):1762-1767. PMID: 21542747.

[3] van den Brand M, Elving LD, Drenth JP, van Kreiken JH. Glycogenic hepatopathy: A rare cause of elevated serum transaminases in diabetes mellitus. Neth J Med 2009; 67(11):394-396. PMID: 20009116.

[4] Mauriac P. Gros ventre. Hepatomegalie. Troubles de la croissance chez les enfants diabetiques traites depuis plusieurs annes par l'insuline. Gaz Hebd Sci Med Bourdeaux 1930; 26:402-410.

[5] Sweetser S, Kraichely RE. The bright liver of glycogenic hepatopathy. Hepatology 2010; 51(2):711-712. PMID: 19957373.

[6] Abaci A, Bekem O, Unuvar T, et al. Hepatic glycogenosis: A rare cause of hepatomegaly in type 1 diabetes mellitus. J Diabetes Complications 2008; 22(5): 325-328. PMID: 18413182.

[7] Hudacko RM, Manoukian AV, Schneider SH, Fyfe B. Clinical resolution of glycogenic hepatopathy following improved glycemic control. J Diabetes Complications 2008; 22(5):329-330. PMID: 18413180.

[8] Munns CF, McCrossin RB, Thomsett MJ, Batch J. Hepatic glycogenosis: Reversible hepatomegaly in type 1 diabetes. J Paediatr Child Heath 2000; 36(5):449-452. PMID: 11036799.

[9] Torbenson M, Chen YY, Brunt E, et al. Glycogenic hepatopathy: An underrecognized hepatic complication of diabetes mellitus. Am J Surg Pathol 2006; 30(4):508-513. PMID: 16625098.

[10] Adams LA, Sanderson S, Lindor KD, Angulo P. The histological course of nonalcoholic fatty liver disease: A longitudinal study of 103 patients with sequential liver biopsies. J Hepatol 2005; 42(1):132-138. PMID: 15629518.

Keywords: liver diseases, glycogen storage, disease, diabetes mellitus, hepatomegaly

CMV Colitis in an HIV Positive Patient with CD4 greater than 200

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Introduction

Cytomegalovirus (CMV) disease typically occurs in immunocompromised individuals including HIV-positive patients with CD4 counts less than 50 cells/μL to 100 cells/μL.[1] Few cases of CMV gastrointestinal disease have been reported in patients with CD4 counts greater than 200 cells/μL.[2-4]

Case Report

A 28-year-old male known to have HIV was admitted with a one-week history of worsening fatigue, nausea, vomiting, 2 kg weight loss, and constipation. Blood pressure was 110/70 mmHg. Heart rate was 105 bpm and body temperature was 37.2 C.

On physical examination, the patient looked dehydrated. His abdomen was tender to palpation without guarding. Bowel sounds were normal. Initial lab work showed sodium at 130 mEq/l, albumin at 2.2 g/dl, and white blood count at 15.9 K/cmm with normal differentials. Blood cultures were negative.

On admission, his CD4 count was 223 cells/ml and viral load was 5350 copies per ml. Three months prior, his CD4 count was 666 cells/ml with 1960 HIV RNA copies per ml. A kidney, ureter, and bladder **(**KUB**)** x-ray study showed small bowel obstruction. A nasogastric tube was inserted. Computed tomography (CT) of the abdomen showed multiple air and fluid filled loops of small bowel with marked edema of distal small bowel. Colonoscopy revealed congested and erythematous mucosa with skip areas within the proximal, middle, and distal transverse colon and congestive mucosa within the terminal ileum with prominent Peyer's patches. Serum cytomegalovirus (CMV) PCR was 3250 IU/mL.

Histological findings in colonic biopsies revealed active inflammation with ulceration (Figure 1) and characteristic large cells (Figure 2). CMV infection could be confirmed immunohistochemically (Figure 3). The patient was started on IV ganciclovir. Highly active anti-retroviral therapy (HAART) was initiated with efavirenz, emtricitabine, and tenofovir.

The patient improved. He was discharged on ganciclovir 450 PO BID and HAART. Three weeks later, the patient was seen at primary care physician's office with clinical improvement and repeat serum CMV PCR was negative.

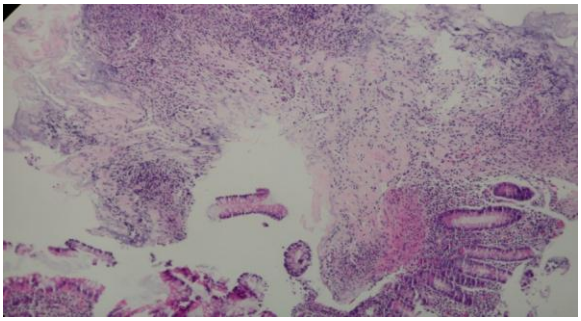

Figure 1. H&E stained section of mucosa with ulceration and inflammation.

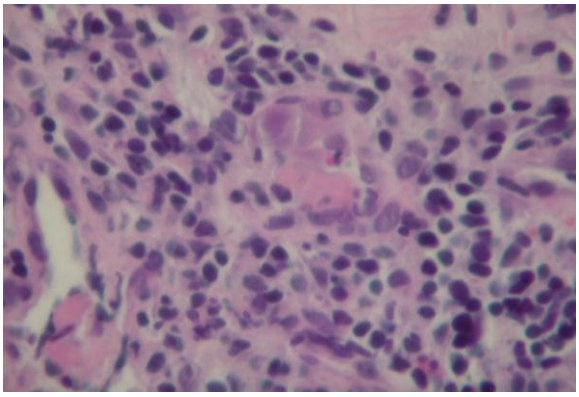

Figure 2. H&E stained section showing 3 large cells with large nucleus, eosinophilic nucleolus, and stippled appearance of cytoplasm admixed with mostly small lymphocytes and a few eosinophils.

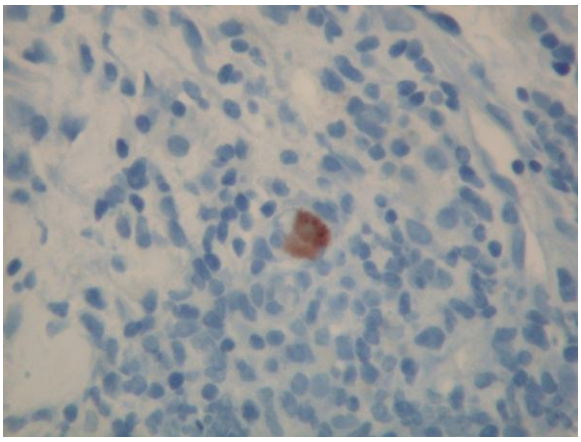

Figure 3. CMV immunohistochemical stain of biopsy.

Discussion

CMV colitis can occur in up to 7.3% of persons with AIDS.[5] CMV colitis occurs late in the course of HIV infection.[6] The risk of opportunistic infections in patients with HIV has been known to be dependent on the degree of immunodeficiency as measured by CD4 T cells. Ulcers caused in the gastrointestinal tract by CMV infection are observed usually when the number of CD4 decreases to less than 50 cells/μL to 100 cells/μL. For example, Wilcox et al.[7] reported CMV colitis in 56 HIV patients, most with severe immunodeficiency and a median CD4 count of 15 cells/μL.

Few cases of CMV colitis in HIV positive patients with CD4 count more than 200 cells/ μL have been reported. Yotsumoto and colleagues[2] reported cytomegalovirus esophagitis and colitis, esophageal candidiasis and colon amebiasis in an HIV patient with CD4 count more than 200 cells/ μL. Wolf and colleagues[3] reported a case of severe CMV colitis in an HIV positive woman with relatively preserved CD4 count. Smith and colleagues[4] reported a case of a patient with CMV colitis and a CD4 count of 800.

Explanations of acquiring CMV colitis with relatively higher CD4 counts include poor nutritional status or alcohol consumption.[8] Our patient denied alcohol abuse. Surawicz et al.[9] reported CMV colitis in immunocompetent individuals as a consequence of receptive anal intercourse. Our patient was a man who had sex with men, so there was possibility of an anal mucosa tear. Another possibility is dysfunction of T cells secondary to HIV virus, although it is difficult to prove.[2]

Conclusion

Although gastrointestinal manifestations of CMV in patients with advanced HIV disease are well described, this case highlighted that CMV colitis also can occur in patients with CD4 counts greater than 200. CMV colitis should be included in the differential diagnosis of any HIV-positive patient presenting with lower gastrointestinal symptoms, regardless of their CD4 counts.

References

[1] Springer KL, Weinberg A. Cytomegalovirus infection in the era of HAART: Fewer reactivations and more immunity. J Antimicrob Chemother 2004; 54(3):582-586. PMID: 15282241.

[2] Yotsumoto M, Nakamura N, Kitano K, et al. Cytomegalovirus esophagitis and colitis, esophageal candidiasis and colon amebiasis in an HIV patient with more than 200/μL CD4 positive lymphocytes. J AIDS Res 2002; 5:153-537.

[3] Wolf T, Bickel M, Faust D, Fellbaum C, Brodt HR. A case of severe CMV-colitis in an HIV positive patient despite moderate immunodeficiency. Scand J Infect Dis 2003; 35(11-12):904-906. PMID: 14723380.

[4] Smith PR, Glynn M, Sheaff M, Aitken C. CMV colitis in early HIV infection. Int J STD AIDS 2000; 11(11):748-750. PMID: 11089790.

[5] Gallant JE, Moore RD, Richman DD. Keruly J, Chaisson RE. Incidence and natural history of cytomegalovirus disease in patients with advanced human immunodeficiency virus treated with zidovudine. The Zidovudine Epidemiology Study Group. J Infect Dis 1992; 166(6):1223-1227. PMID: 1358986.

[6] Mentec H, Leport C, Leport J, Marche C, Harzic M, Vildé JL. Cytomegalovirus colitis in HIV-1-infected patients: A prospective research in 55 patients. AIDS 1994; 8(4):461-467. PMID: 8011249.

[7] Wilcox CM, Chalasani N, Lazenby A, Schwartz DA. Cytomegalovirus colitis in acquired immunodeficiency syndrome: A clinical and endoscopic study. Gastrointest Endosc1998; 48(1):39-43. PMID: 96846 62.

[8] Latif O, Peterson JD, Waltenbaugh C. Alcohol-mediated polarization of type 1 and type 2 immune responses. Front Biosci 2002; 7:a135-a147. PMID: 121338 21.

[9] Surawicz CM, Myerson D. Self-limited cytomegalovirus colitis in immunocompetent individuals. Gastroenterology 1988; 94(1):194-199. PMID: 2826283.

Keywords: cytomegalovirus infections, colitis, HIV, CD4-positive T-lymphocytes

CLINICAL QUIZ

Simultaneous Bilateral Spontaneous Pneumothorax

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A 29-year-old Caucasian male presented with a sharp right-sided chest pain and worsening dyspnea of two days duration. He reported chronic cough with productive, purulent, non-bloody phlegm for two years. He denied fevers, chills, or weight loss. He lived in Kansas and denied foreign travel or incarcerations. He had a 20 pack-years cigarette smoking history. He also routinely smoked marijuana. The patient had leukocytosis with a white blood cell count of 18,400 (neutrophils 73%, lymphocytes 17%, and eosinophils 2%). A chest x-ray (Figure 1a) revealed bilateral spontaneous pneumothorax with complete left lung collapse, moderately large left pleural effusion, and 20% right-sided pneumothorax. A computed tomography (CT) of the chest (Figure 1b) showed diffuse lung cysts, including cystic bronchiectasis, and diffuse tree-in-bud infiltrates in the right lung and large left pleural fluid with absence of identified normal lung tissue. There was no thoracic lymphadenopathy. Two chest tubes were placed, one on each side. A large amount of thick purulent fluid was evacuated from his left chest and sent for cultures.

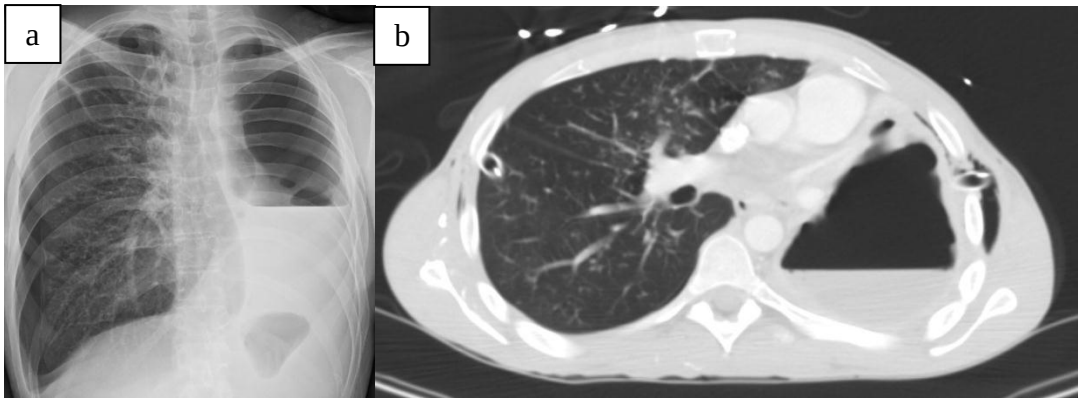

Figure 1. (a) Chest x-ray revealed bilateral spontaneous pneumothorax. (b) CT of the chest showed diffuse lung cysts.

What is the most likely etiology?

A. Pulmonary Langerhans Cell Histiocytosis
B. Mycobacterium Tuberculosis
C. Pulmonary Lymphangioleiomyomatosis
D. Allergic Bronchopulmonary Aspergillosis

Correct Answer: B. Mycobacterium Tuberculosis

Each of the etiologies above have been associated with bilateral spontaneous pneumothorax.[1,2] Pulmonary Langerhans cell histiocytosis usually is diagnosed in young smokers who present with respiratory and constitutional symptoms.[3] CT of the chest shows ill-defined or stellate nodules associated with reticulonodular opacities and upper lung zone cysts or honeycombing. Pulmonary lymphangioleiomyomatosis is suspected in a young female of child bearing age who presents with progressive dyspnea, spontaneous pneumothorax, and chylous pleural effusion.[4,5] Allergic bronchopulmonary aspergillosis should be suspected in asthmatic or cystic fibrosis patients with significant bronchorrhea, eosinophilia, and cylindrical bronchiectasis.[4,5]

Mycobacterium tuberculosis has been reported as a rare cause of simultaneous bilateral spontaneous pneumothorax.[2] Pneumothorax accounts for 0.6% to 1.5% of this unusual radiologic presentation of active Mycobacterium tuberculosis.[6,7] The pneumothorax is believed to be secondary to cavitary formation.[8,9] In our patient, sputum and pleural fluid culture were positive for Mycobacterium tuberculosis. Treatment consisted of antitubercular four-drug regimen, chest drainage, then Video-Assisted Thoracoscopic Surgery (VATS) for the left empyema.

References

1 Sayar A, Turna A, Metin M, Küçükyağci N, Solak O, Gürses A. Simultaneous bilateral spontaneous pneumothorax report of 12 cases and review of the literature. Acta Chir Belg 2004; 104(5):572-576. PMID: 15571026.

2 Graf-Deuel E, Knoblauch A. Simultaneous bilateral spontaneous pneumothorax. Chest 1994; 105(4):1143-1146. PMID: 8162740.

3 Kulwiec EL, Lynch DA, Aguayo SM, Schwarz MI, King TE Jr. Imaging of pulmonary histiocytosis X. Radiographics 1992; 12(3):515-526. PMID: 1609142.

4 Agarwal R, Aggarwal AN, Gupta D, Jindal SK. Aspergillus hypersensitivity and allergic bronchopulmonary aspergillosis in patients with bronchial asthma: Systematic review and meta-analysis. Int J Tuberc Lung Dis 2009; 13(8):936-944. PMID: 19723372.

5 Stevens DA, Moss RB, Kurup VP, et al. Allergic bronchopulmonary aspergillosis in cystic fibrosis--state of the art: Cystic Fibrosis Foundation Consensus Conference. Clin Infect Dis 2003; 37(Suppl 3):S225-S64. PMID: 12975753.

6 Freixinet JL, Caminero JA, Marchena J, Rodríguez PM, Casimiro JA, Hussein M. Spontaneous pneumothorax and tuberculosis: Long-term follow-up. Eur Respir J 2011; 38(1):126-131. PMID: 20947681.

7 Aktoğu S, Yorgancioglu A, Cirak K, Köse T, Dereli SM. Clinical spectrum of pulmonary and pleural tuberculosis: A report of 5,480 cases. Eur Respir J 1996; 9(10):2013-2035. PMID: 8902463.

8 Shamaei M, Tabarsi P, Pojhan S, et al. Tuberculosis-associated secondary pneumothorax: A retrospective study of 53 patients. Respir Care 2011; 56(3):298-302. PMID: 21255490.

9 Mezghani S, Abdelghani A, Njima H, et al. [Tuberculous pneumothorax. Retrospective study of 23 cases in Tunisia.] [French] Rev Pneumol Clin 2006; 62(1):13-18. PMID: 16604035.

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