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Nijmegen Breakage Syndrome-like Disease Complicated by Colon Cancer with Liver Metastasis: A Case Report

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ABSTRACT

Background: Nijmegen Breakage Syndrome (NBS) is a rare autosomal recessive DNA repair disorder that increases the risk of malignant tumors. Colorectal cancer is one of the common malignant tumors, and its liver metastasis presents a focal point and challenge in the treatment of colorectal cancer.

Case Presentation: A 24-year-old male was diagnosed with NBS-like disease complicated by colon cancer with liver metastasis.

Conclusions: Early identification of NBS-like disease is crucial for accurate diagnosis, genetic counseling, cancer screening, risk reduction, and the selection of appropriate anticancer treatments.

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Introduction

Nijmegen Breakage Syndrome (NBS) is a rare autosomal recessive disorder characterized by microcephaly, immunodeficiency, and compromised DNA repair, leading to heightened sensitivity to ionizing radiation and an increased risk of malignancy [1]. The protein encoded by RAD50, in complex with MRE11 and NBS1, binds to DNA and exhibits multiple enzymatic activities required for non-homologous end joining in DNA repair. This complex is crucial for double-strand break repair, cell cycle checkpoint activation, telomere maintenance, and meiotic recombination. Compound heterozygous mutations in RAD50 have been identified in individuals with NBS-like disorders [2-4]. The RAD50 c.2979_2980del p.H993Qfs*6 frameshift mutation in exon 9 of the RAD50 gene results in the 993rd codon changing from histidine to glutamine, introducing a premature stop signal at the sixth position in a new reading frame, constituting a shift mutation. This variant may lead to a loss of normal protein function through protein truncation or nonsense-mediated mRNA decay and is classified as likely pathogenic according to the ACMG guidelines [5, 6]. Malignancy is a common manifestation of NBS and is sometimes the first symptom in heterozygous carriers of NBS pathogenic variants. Among these malignancies, hematologic cancers are the most common, while gastrointestinal tumors are extremely rare [7-9]. Colon cancer is one of the more common malignant tumors, with its liver metastasis representing a key challenge in treatment [10]. Liver metastasis generally carries a poor prognosis and is the leading cause of death in patients with colorectal cancer [11].

We report a case of NBS-like disease complicated by colon cancer and liver metastasis, aiming to explore the potential role of RAD50 germline mutations in these tumors and offer insights for the comprehensive treatment of such complex cases.

Case Report

A 24-year-old man presented to the oncology clinic due to a mixed intrahepatic lesion detected during a physical examination with a color Doppler ultrasound performed one month earlier. An electronic colonoscopy revealed a wide-based, round tumor in the liver flexure, approximately 1.5 x 1.5 cm in size, with a rough and congested surface that bled easily upon contact. Pathological examination showed high-grade intraepithelial neoplasia with carcinomatosis. Immunohistochemical results indicated that cancer cells expressed MSH2 (+), MSH6 (+), MLH1 (+), PMS2 (+), and Ki-67 (90%+). Molecular testing revealed a RAS wildtype and a BRAF V600 wildtype.

Upper abdominal enhanced MRI showed a shallow lesion with unclear borders, measuring approximately 3.8 × 3.2 cm in the S5 segment of the liver,

suggesting a neoplastic lesion with bleeding. The patient underwent laparoscopic liver cancer resection, cholecystectomy, radical colon cancer resection (laparoscopic right hemicolectomy with intraoperative enteroscopy), and abdominal adhesion lysis.

Postoperative pathology revealed moderately differentiated adenocarcinoma. Tumor invasion was classified as T3, with the tumor penetrating the muscularis propria to the serosa/subserosa. A vascular cancer thrombus was present, but no nerve invasion was observed. Both the proximal and distal resection margins were tumor-negative, as were the circumferential resection margins. Of 17 lymph nodes examined, none showed cancer metastasis (0/17).

Adenocarcinoma was also found in segment 5.6 of the liver, and the immunohistochemical results were consistent with colon cancer metastasis. The immunohistochemical findings included CK20 (+), CDX2 (+), SATB2 (+), and Her-2 (1+). The immunohistochemistry results were consistent with colon cancer metastasis. The patient recovered well after surgery, and the incision healed without complications. Based on the patient's imaging, gastrointestinal endoscopy, and immunohistochemical examination, the patient was diagnosed with right colon adenocarcinoma with liver metastasis (T3WOMLa IVA stage, RAS wild type, BRAF V600 wildtype).

The patient then underwent genetic testing, which revealed a RAD50 c.2979_2980del p.H993Qfs*6 frameshift mutation in exon 19. The patient received "oxaliplatin + fluorouracil" as postoperative adjuvant chemotherapy. One month later, a PET-CT scan was performed, and no signs of residual tumor were found. Tumor markers were lower than before.

The patient is unmarried and has no children. His father had lymphoma. The patient was frail during childhood, experiencing recurrent fevers and respiratory tract infections. After the age of 12, the frequency of respiratory tract infections decreased, and he showed no signs of intellectual disability.

Discussion

Malignant tumors are a common clinical manifestation in patients with NBS syndrome and represent the leading cause of death. A retrospective analysis of 84 NBS patients from different regions of Ukraine, spanning from 1999 to 2023, revealed that the most common malignancies among NBS patients were lymphoma, leukemia, rhabdomyoma, and ovarian cancer, with no reported cases of colon cancer [12]. Here, we describe the diagnosis and treatment of a rare case of NBS-like disease complicated by colon cancer with liver metastasis.

With the rapid advancements in molecular biology, precise individualized treatments guided by genetic testing have significantly improved the prognosis of patients with advanced colorectal cancer [13]. In advanced colorectal cancer, the primary genetic markers influencing treatment decisions include KRAS, NRAS, BRAF, and microsatellite instability. Despite these advancements, a subset of patients with rare genetic mutations continues to face a grim prognosis. Particularly challenging are cases involving familial hereditary tumor syndromes arising from identifiable susceptibility germline mutations. For these individuals, clinicians must explore deeper treatment strategies, requiring further investigation and refinement[14, 15].

The identification of a heterozygous RAD50 mutation suggests that the patient is a carrier of NBS-like disease. RAD50, a crucial component of the Mre11-Rad50-Nbs1 (MRN) complex, plays a vital role in detecting and repairing DNA double-strand breaks. Mutations in this gene may compromise DNA repair capacity, thereby increasing cancer susceptibility [16]. Research has shown that RAD50-deficient cells exhibit severe DNA double-strand breaks, heightened cell proliferation, and sustained inflammatory responses, all of which contribute to colon tumorigenesis in RAD50IEC-KO mice treated with azoxymethane (AOM)-DSS [17]. Additionally, RAD50 plays a crucial role in human bone marrow and immune cell function. Mutations in this gene can result in bone marrow failure and impair the development and function of B lymphocytes [18, 19]. We suspect that defects in DNA repair mechanisms and immune surveillance in patients of NBS-like disease may contribute to colon cancer development and progression, as well as an increased risk of liver metastasis.

The first-line standard treatment for advanced right-sided colon adenocarcinoma with wild-type RAS and BRAF V600E mutation is oxaliplatin combined with fluorouracil chemotherapy. Oxaliplatin is a DNA intra-chain cross-linking agent whose cytotoxic effects rely on double-strand breaks (DSBs). In cases of defective DSB repair, the chemotherapy efficacy of oxaliplatin may be enhanced [20]. Several studies have indicated that although NBS is an autosomal recessive disease, heterozygous carriers have a higher cancer risk and increased sensitivity to radiation [21]. This may explain the presence of liver metastasis at our patient's initial diagnosis, which has significant implications for treatment decision-making. If the patient develops skin metastasis or chemotherapy resistance, external radiotherapy may be a viable and effective treatment option with minimal side effects. However, these conclusions require validation through larger-scale studies.

Despite the increasing accessibility of genetic testing, the rate of genomic screening among colorectal cancer patients remains suboptimal. As a result, a significant proportion of germline mutation carriers

remain undiagnosed, hindering the implementation of precision medicine and cancer prevention strategies. Establishing molecular genetic diagnostics for this syndrome is crucial for the optimal clinical management of patients, as it aids in tumor prevention and addresses complications associated with congenital combined immunodeficiency in NBS-like disease. Raising awareness and increasing research focus on NBS remain essential in our pursuit of improved patient outcomes.

Conclusion

Although no established guidelines exist for gastrointestinal cancer screening in NBS-like disease, our case underscores the importance of genetic evaluation in young patients presenting with tumors and metastases. Since NBS often manifests before adulthood and cancer remains its leading cause of mortality, early recognition is critical for accurate diagnosis, genetic counseling, and cancer screening. Early detection facilitates risk reduction and optimizes anticancer treatment selection. Unfortunately, since the patient's parents and siblings did not undergo genetic testing, it remains uncertain whether they carry cancer susceptibility genes. Colorectal cancer develops from precancerous polypoid lesions; therefore, early detection through endoscopic screening and timely removal of precancerous lesions are essential [22]. Family members are advised to undergo regular health check-ups, including tumor marker testing and colonoscopy, to facilitate early detection and preventive measures.

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Table 1 Genetic Testing Results of the Patient

Overview of Genetic Variation	Mutated genes	15 Somatic mutations, 1 Germline mutation
Targeted Therapy-related Gene Mutations	Somatic variants of clear or potential clinical significance (5)	TP53 c.524G>A p.R175H Exon 5 missense mutation
		TP53 c.455C>T p.P152L Exon 5 missense mutation
		APC c.2313_2314del pE771Dfs 3* Exon 16 frameshift mutation
		APC c.4285C>T p.Q1429 * Exon 16 stop codon acquired mutation
		FGFR1 Copy number expansion 5.8
	Pathogenic or likely pathogenic germline variants (1)	RAD50 c.2979_2980del p.H993Qfs*6 Exon 19 frameshift variant
Immunity Targeted Therapy-related Gene Mutations	PD-L1	TPS 1%
	PD-L1	CPS 8
	MSI	MSI-L 2.01%
	TMB	TMB-M 7.0Muts/Mb
	Positively correlated gene variants	Not Detected
	Negatively correlated gene variants	Not Detected
	POLE/POLD1(Exonuclease domain mutations)	Not Detected
Pathogenic or likely pathogenic germline variants (1)	Prognostic markers (4)	TP53 c.524G>A p.R175H Exon 5 missense mutation
		TP53 c.455C>T p.P152L Exon 5 missense mutation
		APC c.2313_2314del pE771Dfs*3 Exon 16 frameshift mutation*
		APC c.4285C>T p.Q1429 Exon 16 stop codon acquired mutation

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