

Introduction

Hereditary multiple exostoses (HME) is an autosomal dominant disorder characterized by the growth of multiple bony tumors. These tumors include benign osteochondromas and less commonly, malignant tumors that arise from transformation of exostoses into secondary osteosarcomas and chondrosarcomas [1,3]. There have been no reported cases of lymphoma in the pediatric HME population. We report a case of a 10 year old boy with HME who developed Burkitt lymphoma of the abdomen.

Case Report

A 10 year old boy with HME presented with five days of abdominal pain, distention, and vomiting. His medical history was remarkable only for several orthopedic procedures throughout childhood for osteochondromas (**Images A, B**). The resected tissue was always consistent with HME (**Images C, D**). His family history was significant for three first degree relatives with HME.

A



Multiple osteochondromas bilaterally

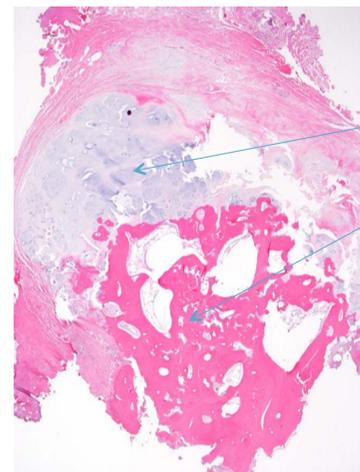
B



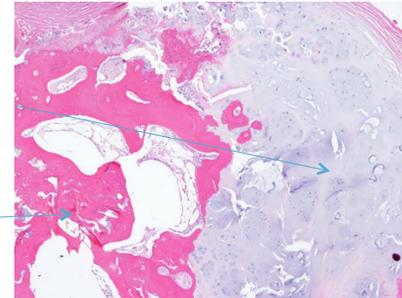
Large osteochondroma in right humerus

Case Report (cont.)

C



D



Cartilage cap
Bone

Biopsy from osteochondroma: histology shows cartilage-capped bony tissue, consistent with osteochondroma

Computed tomography (CT) at presentation demonstrated thickened and edematous bowel wall, a soft tissue mass involving the peritoneum anterior to the stomach and liver, two hypodense lesions in the liver, and ascites. Tissue biopsy confirmed Burkitt lymphoma. Bone marrow biopsies/aspirates and cerebrospinal fluid were negative for malignancy. He was diagnosed with stage III Burkitt lymphoma of the abdomen and liver. The patient was treated on the ANHL01P1 chemotherapy protocol for non-Hodgkin lymphoma. Treatment was complicated by acute renal failure requiring short-term hemodialysis secondary to severe tumor lysis syndrome and multiple infections while neutropenic. He was not treated with radiation therapy. He was in complete remission 3.5 months later after completion of chemotherapy and is alive and free of disease eight years later.

References

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Discussion

Hereditary multiple exostoses (HME) is an autosomal dominant disorder associated with growth of multiple osteochondromas. Patients with HME can be considered to have a tumor predisposition syndrome since they have an increased risk for both benign and malignant tumors. The most common neoplasms in HME are benign osteochondromas and malignant chondrosarcomas and osteosarcomas, which usually arise from long standing osteochondromas [3,4]. The overall lifetime risk of sarcomas in HME patients varies between 2-4% [5].

Far less common in HME patients are non-sarcomatous malignancies. To our knowledge there have been no reported cases of high-grade lymphoma in the pediatric population outside of this case report. [1,2]

The typical neoplasms in HME arise from germline mutations in the *EXT* family of genes. Two of the genes identified, *EXT1* and *EXT2*, are glycosyltransferases that synthesize heparan sulfate (HS). Interestingly, HS also has important roles in the growth, invasiveness and metastatic behavior of some tumors [4,10]. *EXT1* and *EXT2* are both likely tumor suppressor genes based on their role in exostosis formation and confirmed by the loss of heterozygosity in HME-related and sporadic sarcomas [4]. Mutations in *EXT1* and *EXT2* are responsible for the majority of multiple exostoses and are found in most osteosarcomas and chondrosarcomas [2,4]. The study of patients with HME provided the first direct evidence linking an aberrant HS structure to tumorigenesis [9].

Unlike tumors found in HME, sporadic osteochondromas and chondrosarcomas usually do not have mutated *EXT* genes. However, the *EXT* genes may still play a role in sporadic oncogenesis when hypermethylation occurs in the gene's CpG islands promoter region. This effect can be reversed with demethylating agents [4]. Demethylating agents might therefore have a role in treatment of *EXT*-hypermethylated acute leukemias [4].

Conclusion

- HME is a tumor predisposition disorder
- Osteochondromas, osteosarcomas, and chondrosarcomas are the prototypical neoplasms seen in HME
- We describe the first case of high grade lymphoma in a pediatric patient with HME (patient is disease-free eight years later)
- Molecular biology of HME might provide insight into new treatment options for pediatric lymphoma