Autopsy Case Reports

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Pleomorphic undifferentiated soft tissue sarcoma in patient with long standing inflammatory bowel disease

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ABSTRACT

Inflammatory bowel disease (IBD) has been associated with the development of both gastrointestinal and extraintestinal malignancy. The role of therapy in the development of malignancy in IBD has been controversial. We present the case of a 40-year-old female patient with long-standing mild IBD, who developed an undifferentiated pleomorphic sarcoma of the inguinal region and provide a brief review of the relevant literature. While our case likely represents a coincidence of two unrelated pathological entities, clinicians should keep in mind the possibility of soft tissue sarcomas in patients chronically treated with anti-inflammatory agents.

Keywords
Crohn Disease; Sarcoma; Anti-inflammatory Agents; Neoplasms, Second Primary

INTRODUCTION

Undifferentiated pleomorphic sarcoma (UPS), formerly known as malignant fibrous histiocytoma, is a genome unstable soft tissue or bone neoplasm that can arise from any part of the body. While most cases represent a dedifferentiated form of leiomyosarcoma and liposarcoma, in a minority of cases no evidence of differentiation can be found.[1] Most undifferentiated high-grade sarcomas occur in patients over age 40, and have a less aggressive clinical course compared with more differentiated tumors.[2] While the majority of sarcomas seem to arise without a predisposing factor, irradiation, immunosuppression, exposure to certain chemicals, viral infection and germline mutations have been implicated as etiologic factors in some types, with radiotherapy specifically being linked to UPS.[1]

Inflammatory bowel disease (IBD) has been associated with an increased risk of development of gastrointestinal as well as extraintestinal malignancies.[3,4] The gastrointestinal cancers include colon and small bowel adenocarcinoma, cholangiocarcinoma and anal squamous cell carcinoma. The pathogenesis of these cancers is linked to the prolonged inflammation characteristic of IBD. Evidence supports an increased risk of extraintestinal malignancies including lymphomas,[5] non-melanoma skin cancer,[6] urothelial cancer[7] and HPV (human papilloma virus)-related cervical cancer. The excess risk of extraintestinal malignancies has been attributed to IBD treatment modalities, namely systemic immunosuppression using thiopurines, corticosteroids,

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methotrexate and anti-tumor necrosis factor (anti-TNF) antibodies.[5]

Patients with IBD might also have an increased risk of developing thyroid,[8] breast,[9] and oral cancer[10] although the potential underlying mechanisms remain unknown. Several case reports[11-13] of sarcomas arising in the context of immunosuppressant therapy for IBD have raised the question whether an increased risk for the development of soft tissue tumors exists in IBD patients.

CASE REPORT

A 40-year old woman was admitted to our hospital for evaluation of a rapidly growing, painless inguinal mass of four-month duration. She was a smoker with long-standing Crohn's disease diagnosed at age 20, with mild remitting gastrointestinal symptoms, responsive to therapy with topical and systemic 5-aminosalicylic acid. She has been in remission for 5 years at the time of the present complaint. She also developed a concomitant autoimmune thyroiditis.

The physical examination showed a palpable, hard, mobile nodule in the left inguinal region. On ultrasound examination, a hypoechoic formation measuring 30 mm in greatest diameter was found. The tumor was located in the soft tissues distal to the lymphatic inguinal region. A lymph node lesion was suspected, and fine needle aspiration cytology showed poorly differentiated tumor cells resembling melanoma (Figure 1). However, a detailed history and dermatologic exam revealed no evidence of skin lesions.

An additional excision biopsy showed a well-circumscribed tumor with a fleshy cut surface with foci of hemorrhage and necrosis. On microscopic examination, the tumor consisted of anaplastic and pleomorphic cells, with atypical mitoses and invasion of surrounding adipose tissue. Immunohistochemically the neoplastic cells showed strong positivity for vimentin, while CD 34, smooth muscle markers (smooth muscle actin, h-caldesmon, myogenin), melanoma markers (HMB 45, melan A, S 100), vascular markers (CD 31, CD 34), CD 68, MDM 2 and cytokeratin were negative (Figure 2).

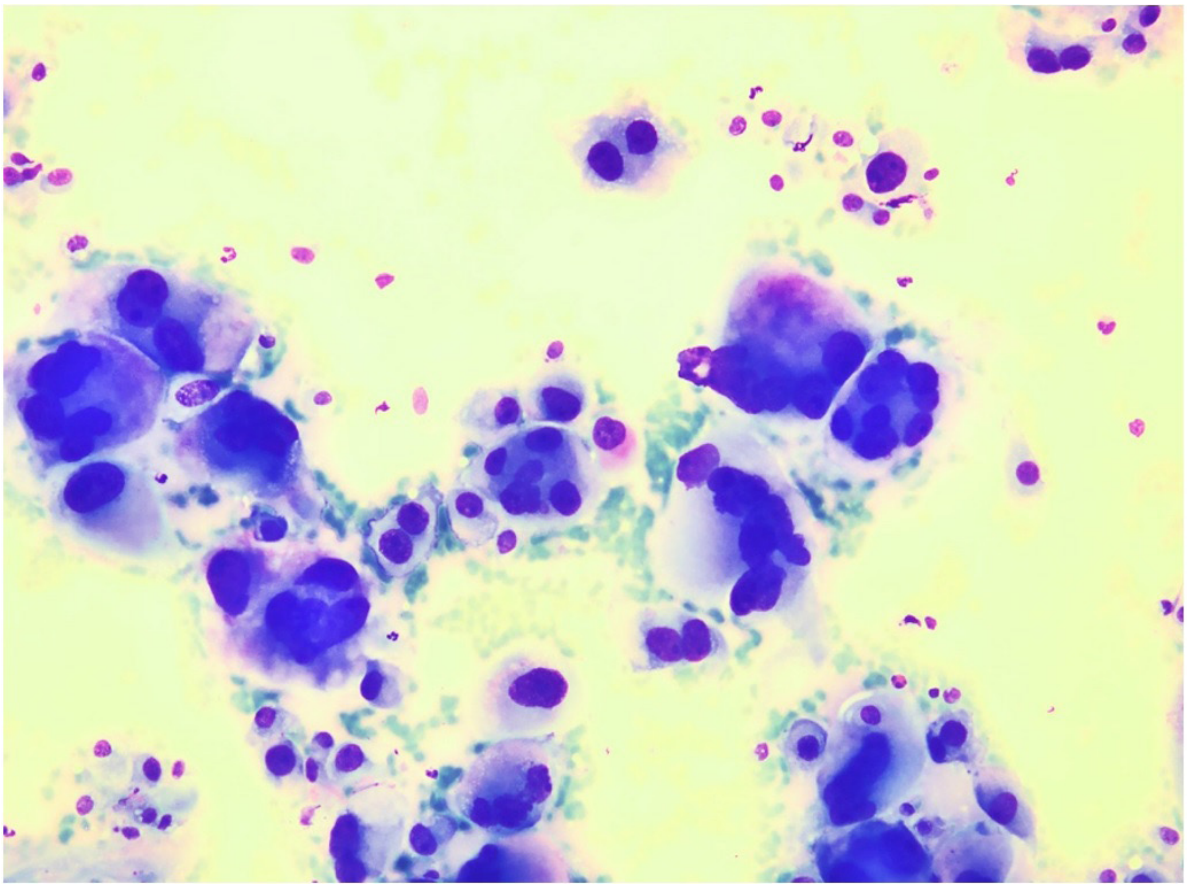

Figure 1. Photomicrography of the fine needle aspiration showing poorly differentiated tumor cells.

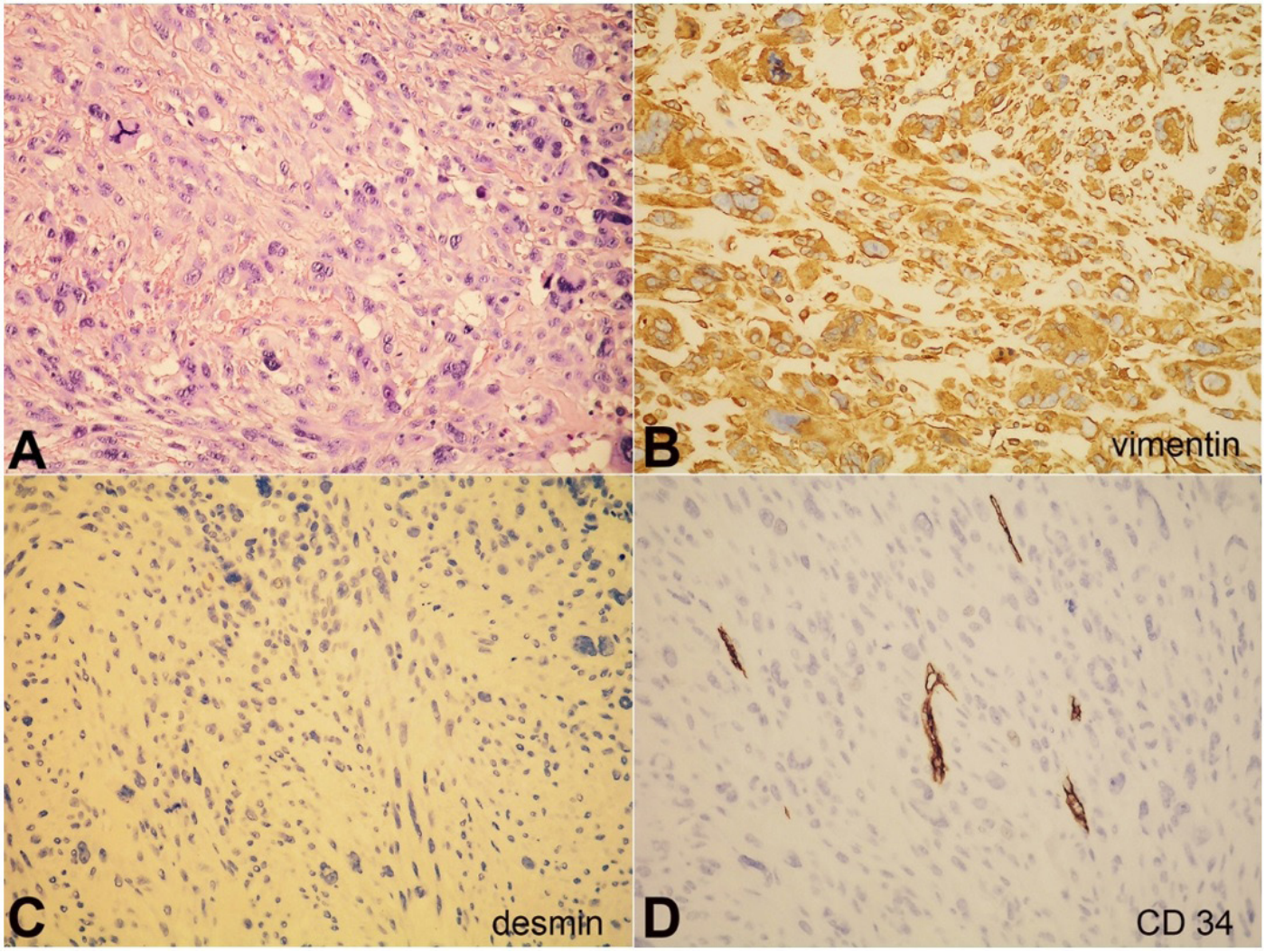

Figure 2. Photomicrography of the biopsy specimen showing in **A –** anaplasia and atypical mitotic figures (H&E, 200x); in **B –** diffuse immunohistochemical positivity for vimentin (200x), and negative for desmin in **C** (200x) and CD34 in **D** (200x).

By the microscopic and immunohistochemical analysis, a diagnosis of exclusion of high-grade, undifferentiated pleomorphic sarcoma was made. Sample margins were positive, and re-excision was performed, with histology showing foci of deep residual tumor.

Her treatment included local radiotherapy, and at 10 months of follow up, she is disease free.

DISCUSSION

IBD therapies have been implicated in the pathogenesis of malignancy. Anti-TNF antibodies and thiopurines have been associated with the development of lymphoproliferative disorders,[14] while thiopurines alone have been shown to increase the risk of non-melanoma skin cancer.[6] Prolonged immunosuppression might ostensibly hinder immune system control of cancerous cells, thereby accelerating tumor growth. Anti-TNF antibodies have been shown to promote neoplastic cell survival via the nuclear factor kappa B (NF-kB) pathway, while thiopurines are implicated in the pathogenesis of lymphomas related to a reactivation of latent Epstein-Barr virus (EBV) infection.[14] Case reports of Kaposi sarcoma in immunosuppressed IBD patients have been published, with a reactivation of underlying human herpes virus 8 (HHV-8) infection postulated as a possible cause.[15-17]

Genome-wide association studies have not found a possible genetic link between IBD and predisposition to malignancy.[18] A link between inflammation and sarcoma development, however, is supported by

a growing body of evidence,[19] including studies of inflammatory malignant fibrous histiocytoma, in which altered hypoxia-induced factor 1 (HIF-1) and NF-kB signaling might play a role.[19]

In a recent retrospective cohort study, a 10-fold increase in the risk of oral cancer was found among IBD patients. Out of the 11 cases, 3 were reported as sarcoma.[10] No association with immunosuppressive therapy was reported. In our case, no prolonged systemic immunosuppressive therapy was needed to control IBD symptoms, and the patient was symptom-free for 5 years before her sarcoma diagnosis.

Our case is the first published concurrence of undifferentiated pleomorphic sarcoma and IBD, and although it likely represents a coincidence of two unrelated pathological entities, clinicians should be aware of the possibility of soft tissue malignancy in IBD patients, especially in the setting of poorly controlled disease requiring prolonged immunosuppression.

The possible association of mesenchymal malignancies and IBD is poorly understood, and further, more detailed studies are needed to shed light on this question.

This case report is in accordance with the Ethics Committee recommendations of "Sestre milosrdnice" University Hospital Centre.

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