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Intestinal Behçet's Disease Presenting as a Tumor on CT-Scan: A Report of an Intriguing Case

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Authors' contributions

This work was carried out in collaboration among all authors. Author IP designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors KC, IN, KN and HT managed the analyses of the study and the literature searches. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Introduction: Behçet's Disease is a multisystem vasculitis of unknown origin that may affect any organ, causing small-vessel vasculitis. Given that there is no specific test, the diagnosis BD is based on clinical criteria. When the gastrointestinal tract is affected, it presents usually with abdominal pain. In case of surgical treatment, the histopathological examination usually reveals small vein vasculitis and nonspecific inflammation. Otherwise, corticosteroids and immunosuppressive drugs are used. In this report, we present a case of Intestinal Behçet's Disease showing features of malignancy on CT-scan.

Case Presentation: A 67-year-old woman, with known history of oral BD under treatment, presented at the Emergency Department complaining of low-grade fever and pain at the right iliac fossa. CT scan revealed a possible tumor in the caecum and partial stenosis of terminal ileum. Right hemicolectomy and right adnexectomy were performed. On gross examination an area of flattened caecal mucosa was revealed, the microscopical examination of which revealed extensive

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mucosal ulceration, transmural inflammation and abscesses. Furthermore, there was marked oedema and many congested vessels all over the intestinal wall as well as in the fallopian tube and ovary. All these findings, in combination with patient's history and the rest of clinical, imaging and laboratory tests lead us to the diagnosis of Intestinal Behçet's Disease.

Conclusion: BD is an autoimmune disorder that may involve the gastrointestinal tract. The diagnosis of this disease should be based on clinical criteria since the results of laboratory or radiological investigations are not specific and may indicate erroneously other conditions.

Keywords: Behçet's disease; vasculitis; small-vessel; intestinal.

ABBREVIATIONS

BD : Behçet's Disease
CMV : Cytomegalovirus
CT : Computed Tomography
HIV : Human Immunodeficiency Virus
HSV : Herpes Simplex Virus
GI : Gastrointestinal
ICBD : International Criteria for Behçet's Disease
ISG : International Study Group
TNF : Tumor Necrosis Factor

1. INTRODUCTION

BD is a chronic, multisystem vasculitis of unknown origin which may affect any organ system. Since there is no specific test or examination, the diagnosis is based on clinical criteria determined by ISG and revised by ICBD [1]. The GI system may also be involved, with the lower GI tract being most commonly affected. BD is characterized by recurrent attacks affecting the mucocutaneous tissues, eyes, joints, blood vessels, brain and gastrointestinal tract. It is most frequently seen in countries along the ancient silk road, from Eastern Asia to the Mediterranean Basin. Young adults between the second and fourth decades of life are mainly affected, with abdominal pain being the most common symptom [2]. The illness develops more frequently in the ileocecal region and demonstrates ulcerations that may penetrate or perforate the bowel wall. Esophageal and gastric ulcerations are rarer occurrences. Bowel wall thickening is the most common finding on computed tomography (CT) scan, possibly similar to other conditions such as IBD or neoplasms [3]. In case of a surgical treatment, the histopathological examination of the resection specimen usually reveals a vasculitis that mainly involves small veins or, alternatively, nonspecific inflammation. Corticosteroids, with or without coadministration of other immunosuppressive drugs, are used in the treatment of severe ocular disease. Their use in intestinal disease is largely empirical. Surgery may be required in case of perforation. BD runs a chronic, unpredictable course with exacerbations and remissions which decrease in frequency and severity over time. Death is mainly the result of major vessel disease and neurological [4].

2. CASE PRESENTATION

We report a case of a 67-year-old woman, who presented at the Emergency Department complaining of low-grade fever (~ 38^{o}C) and abdominal pain localized in the area of the right iliac fossa, for the previous 10 days. The patient has a known history of oral BD, arrhythmia, appendicectomy and adhesiolysis for salpingeal adhesions; she is a smoker (48p/year) and is under a treatment of colchicine, anticoagulants (trifluzal), calcium channel blockers (lercanidipine) and beta-1 blockers (bisoprolol). The clinical examination revealed sensitivity to deep palpation of the right iliac fossa and present intestinal sounds. The laboratory investigations included a full blood count and several biochemical examinations. Also, abdominal x-ray, ultrasound and CT-scan were performed. The latter revealed a lesion in the caecum—possibly of malignant neoplastic nature—with accompanying stenosis of the ileocecal valve and partial ileal obstruction. The patient was admitted to one of our hospital's surgical departments on an emergency basis and underwent a right colectomy and adnexectomy. She fully recovered without complications and was discharged in a good general condition with instructions to continue being monitored by her rheumatologist.

A right hemicolectomy and right adnexectomy specimen were sent to our Pathology Laboratory, comprising of a 4.5 cm long segment of terminal ileus and a 16 cm long segment of large bowel (caecum and ascending colon), connected through the ileocecal valve. Alongside the bowel, perienteric and pericolic fat has also been excised, focally demonstrating a deep-red hue

and whitish exudates on the area of caecum, the latter measuring 6,5x5,5cm. Additionally, the perienteric fat was adjoined with the ipsilateral (right) fallopian tube (length: 4cm, perimeter:1.1cm) and ovary (4.5x2x1cm). The opening of the specimen revealed an area of an oval, flattened and centrally ulcerated area, corresponding to the aforementioned deep-red hued area of the caecal external / serosal surface. There was also thickening of the ileal wall with moderate narrowing of the lumen. Moreover, 4,5 cm distal to the ileocecal valve, on the caecal mucosa, a 0.6 cm large polypoid mass with a short stalk was found. The rest of the small and large bowel mucosa was mildly flattened, without features suggesting a neoplastic disease. In the perienteric and pericolic fat, eight lymph nodes were found, measuring from 0,1 cm to 0,8 cm.

The microscopical examination of the sections from the flattened area of caecal mucosa showed extensive ulceration of the mucosa, moderate to marked architectural distortion of the crypts, moderately to severely diminished mucus production, as well as marked cryptitis. The lamina propria contained a high number of lymphocytes, eosinophils and fewer neutrophils [Fig. 1]. The inflammation was transmural, spreading as far as the serosa, creating abscesses all through the bowel wall. Furthermore, there was marked oedema as well as many congested small vessels in the mucosa and submucosa and subserosa, that showed evidence of vasculitis [Fig. 2]. The rest of the small and large intestine included the region of thickened ileal wall, as well as the surgical margins of the specimen, demonstrated mild, non-specific, chronic inflammation and transmural vascular congestion. The ordered histochemical stains (Gram, Giemsa, PAS, Ziehl-Nielsen) did not demonstrate any growth of microorganisms. Possible CMV or HSV infection was also excluded morphologically and immunohistochemically. All lymph nodes found in the perienteric and pericolonic fatty tissue demonstrated moderate reactive changes. Other findings included the polypoid mass at caecum with histological features of tubular adenoma with low-grade (mild) dysplasia. Finally, sections from the fallopian tube demonstrated mild fibrosis of the fimbriae, whereas absence of ovarian follicles, dense cellular stroma with multiple corpora albicantia and many congested, thick-walled vessels were observed in the sections obtained from the ovary.

Given the extension of inflammation and small vessel vasculitis, in combination with patient's history and the other clinical, imaging and laboratory findings, the diagnosis of Intestinal Behçet's Disease was established. Patient remains under treatment after surgery without presenting any other symptom.

3. DISCUSSION

BD is a multi-organ disorder with a higher prevalence in Central Asia, the Middle East, and the Mediterranean Sea, with the mean age of onset being the 3rd and 4th decades of life. In the Mediterranean Basin, Middle Eastern and Asian countries it is more frequently found in men, whereas there is higher female prevalence in the United States, Northern European and East Asian countries in Central Asia [5]. It manifests with aphthous stomatitis, genital ulcers, relapsing iritis, arthritis, skin lesions and vascular disease. However, it may also involve the gastrointestinal tract, central nervous system and cardiovascular system [6]. Although the etiology of Behçet's disease is not clearly identified, the pathogenesis of the disease is most commonly hypothesized as a profound autoimmune inflammatory response triggered by an infectious agent in a genetically susceptible host. As there are no single specific manifestations or diagnostic tests, various diagnostic criteria have been proposed around the world with the ISG criteria, revised by ICBD, being the most commonly used. The ISG criteria include the following five clinical presentations: The first two are oral aphthosis and genital aphthosis. The third criterion is skin lesions, comprising of pseudofolliculitis and/or erythema nodosum. The fourth one is ocular lesions (anterior uveitis, posterior uveitis, and retinal vasculitis). The fifth criterion is the presence of the "pathergy phenomenon". Based on the ISG criteria, the presence of oral aphthosis, plus two more of the remaining four criteria is mandatory to diagnose BD. Concerning the international criteria, the ICBD added vascular manifestations to the five ISG criteria. Vascular manifestations are defined as superficial phlebitis, deep vein thrombosis, large vein thrombosis, arterial thrombosis, and aneurysm. For ICBD, genital aphthous lesions and eye lesions have more diagnostic value than the other criteria and they get 2 points each. The remaining criteria get one point each. A patient needs to get 3 or more points to be diagnosed/classified as having BD [7].

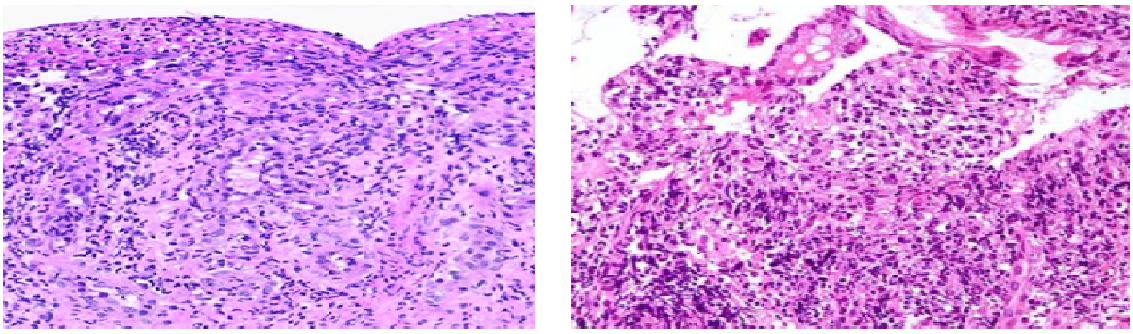

Fig. 1. Flattened area of caecal mucosa with extensive ulceration of the mucosa, marked architectural distortion of the crypts and depletion of mucus production, as well as marked cryptitis. The lamina propria contained a high number of lymphocytes, eosinophils and fewer neutrophils (Hematoxylin – Eosin Stains 100x)

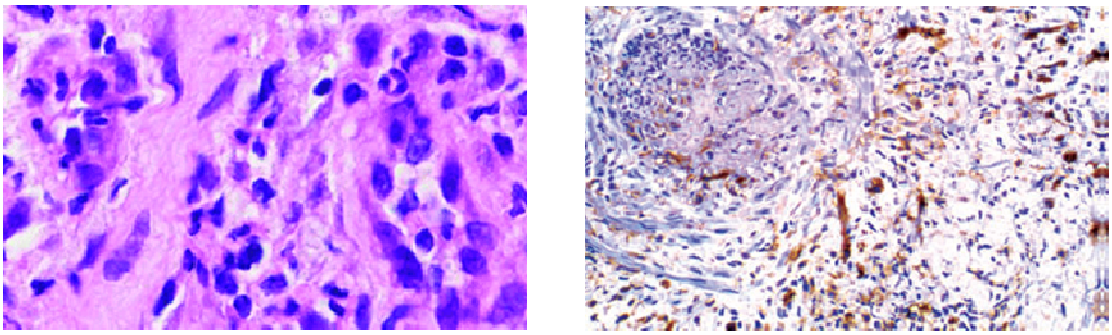

Fig. 2. Small-vessel vasculitis demonstrated in Hematoxylin – Eosin Stain (400x) [left side] and CD31 immunohistochemical assay (100x) [right side]

BD does not follow the principles of Mendelian inheritance, even though occurrence within families has been reported. The correlation between BD and the HLA–B51/B5 genotype, as well as its presence in populations of various ethnicities, strongly suggests that this allele may be a primary and causal risk determinant for BD. [8]. Besides the HLA-complex, associations at non-HLA regions, with IL10 and IL23R-IL12RB2 genes have also been reported [9]. Non-HLA genetic associations, such as endoplasmic reticulum aminopeptidase 1 (ERAP1), interleukin 23 receptor (IL23R) and IL10 variations suggest that BD shares susceptibility genes and inflammatory pathways with other rheumatic diseases, such as spondylarthritis [10].

The clinical expression of Behçet's disease is heterogeneous and the treatment should be individualized based on the organs involved, the severity of the disease, and the patient's medical history. The choice of therapeutic agents is limited by the lack of clinical trials and is largely based on case reports, case series, and several open-label clinical trials. As mentioned, Behçet's disease may affect any part of the GI tract. The involvement of the digestive system is of great significance since it is related to high mortality and morbidity rates. GI manifestations frequently appear 4,5 to 6 years after the onset of oral ulcers [11]. Symptoms usually include nausea, vomiting, diarrhea, severe abdominal pain and bleeding [12]. The ileocaecal region is most commonly affected; however, any part and organ of the GI system may be affected [13]. There is no specific laboratory test for BD and patients may show elevated CRP, EST, IgD, IgA and complement levels. The pathergy test is also performed. Antinuclear antibodies and the rheumatoid factor are usually not found, as is the case with other diseases, such as IBD and pyoderma gangrenosum [14]. Anti-Saccharomyces cerevisiae antibodies (ASCA) positivity can be found in up to 44% of the patients with intestinal BD, but only in 3 to 4% of the patients with non-intestinal BD and in 9% of the healthy control subjects. ASCA positivity is associated with an increased rate of surgical

interventions. The 2 Alpha-enolase antibody has also been detected in patients with BD and may be associated with the disease activity and severity.

Histologically, there are two manifestations of intestinal Behçet's disease: a) Neutrophilic phlebitis, which causes inflammation and ulceration (aphthous or punched out ulcers) of the mucosa and b) Large vessel disease, which results in ischemia and, consequently, infarction [15].

The differential diagnosis includes infectious colitis caused by Entamoeba spp. or Mycobacterium spp., intestinal tuberculosis and infections from viruses such as HIV, HSV or CMV. Non-infectious causes of intestinal inflammation such as Drug-induced colitis, Inflammatory Bowel Disease (Crohn's Disease) and other rheumatic diseases may have to be considered [5,10,16-18]. Malignant neoplasms may also be included in the differential diagnosis, taking into consideration that the radiological image of intestinal BD may simulate neoplasms [19].

Corticosteroids, colchicine, 5-ASA,Thalidomide and traditional immunosuppressive agents, including azathioprine and cyclosporine have been used for the treatment of Behçet's disease. Recently, TNF inhibitors have become available for several rheumatic diseases. Considerable published data suggest that they represent an important therapeutic advance for patients with severe and resistant BD, as well as for those with contraindications or intolerance to the other treatments.

4. CONCLUSION

BD is an autoimmune disorder that may involve the gastrointestinal tract. The clinical, laboratory, radiologic and endoscopic findings may overlap with other infectious, autoimmune or neoplastic diseases and the diagnosis of this disease should be based on clinical criteria.

CONSENT AND ETHICAL APPROVAL

As per university standard guideline, participant consent and ethical approval have been collected and preserved by the authors

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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