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LETTERS TO THE EDITOR

Diagnostic dilemma between intestinal Behçet disease and inflammatory bowel disease with pyoderma gangrenosum

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TO THE EDITOR

I have read with great interest the very recent article titled "Intestinal Behçet's disease with pyoderma gangrenosum: A case report" of Nakamura T *et al* that was published in your journal. The authors stated that they presented a very rare case of intestinal Behçet's disease with pyoderma gangrenosum in a 16-year old patient. However, I would like to make some important contributions and suggestions to the presented case and have a few questions to ask the authors.

First, the exact diagnosis of Behçet disease in a single case depends first on the recognition of a characteristic set of sufficient symptoms and/or signs to allow the physician to diagnose with various levels of certainty from "complete or definitive" Behçet disease to "suspected or possible" Behçet disease[1] based on the clinical sign constellation in Japanese Behçet Disease Research Committee Criteria, the preferred diagnostic criteria before 1989[2]. According to the criteria, such a "complete" or "definitive" diagnosis of Behçet disease needs either at least three major criteria or two major criteria (one of which is ocular disease) or two major criteria associated with 2 minor criteria. This means that the correct diagnosis of Behçet disease can be established only on the basis of aforementioned strict rules that need the complete fulfillment of the criteria with careful differential diagnosis from other etiologies. Therefore, the authors' statement that "she was diagnosed with intestinal Behçet' s disease by the presence of cutaneous pathergy together with two major criteria (oral and genital aphthoses) and one minor criterion (gastrointestinal manifestations) in 1984" cannot be accepted as the presented case does not fulfill the requirements of "Japanese Behçet Disease Research Committee Criteria", the preferred diagnostic criteria in that period, in which cutaneous pathergy is not included in the major or minor criteria. Although oral aphthous and genital ulcerations with a positive pathergy test of the presented case meet the diagnostic criteria of International Study Group[3], published in 1990, however, diagnosis and surgical intervention of the presented case with "incomplete diagnosis" were made in 1989. In other words, the case can be accepted as "suspected" Behçet disease according to the Japanese criteria, provided that other etiologies for these manifestations have been strictly ruled out including inflammatory bowel disease (IBD). Therefore, the authors should first clarify this diagnostic confusion.

Second, the presented case was stated to have colitis involving the entire colon demonstrated by colonoscopy. However, typical intestinal involvement in Behçet disease is characterized mainly by changes in the small intestine or ulcerative lesions at the terminal ileum or cecum, resulting in various digestive symptoms[4]. I think the differential diagnosis was not performed strictly enough in this single case as the aforementioned symptoms are seen in IBD, namely Crohn's disease and ulcerative colitis that need careful evaluation. Although the resected specimen demonstrated severe inflammation with neutrophil accumulation, this is a general finding in inflammatory diseases and intestinal Behçet disease is often indistinguishable from IBD by histological evaluation. Therefore, such a general finding cannot be used as the histological hallmark of intestinal Behçet disease as its diagnosis is based on the presence of deep colonic ulcerations frequently situated in healthy mucosa along with the presence of an adjacent non-specific inflammatory infiltrate affecting the entire colonic wall that is characterized by leukocytoclastic vasculitis and perivasculitis of the arteries and veins with signs of fibrinoid necrosis. Moreover, there is not any knowledge in the presented article about the presence or absence of granulomatous or non-granulomatous changes or caseation with or without confluent (diffuse) or skipping

(segmental) lesions (*i.e.*, mural thickening) that strongly need strict differential diagnosis of intestinal Behçet disease from IBD. Indeed, ulcerative colon, for instance, is restricted to the colon, and exhibits proximal extension over time with full thickness involvement in case of toxic megacolon[5]. Therefore, nothing in the article can exclude these questions in that single case that seems to need clarification.

Third, the authors stated that the patient received 20 mg oral prednisolone treatment for a month, though cutaneous and intestinal lesions of the girl were poorly controlled. However, to our knowledge, corticosteroids (CSs) alone are not used for the treatment[1] and management[6] of Behçet disease at least in the used dose, and no study has found that CSs alone are effective on any symptom or sign as well as on any etiological factors including cutaneous and intestinal lesions that are accused for the pathogenesis of Behçet disease[7-13]. Moreover, CSs are of little value for the maintenance of remission. Indeed, the results of Mat C *et al*[14] are important and demonstrate that CSs alone for about a six- month duration are not effective even on oromucocutaneous symptoms despite the well-known underlying vasculitic pathology of the condition. Because most of the treatments have been shown to work in Behçet disease or in IBD, the used dose of CSs seems not sufficient for such a severe intestinal involvement in the present case and therefore, the patient should have been treated first with a higher dose of CSs (1-2 mg/kg prednisolone per day) for a short time with some other immunomodulating/immunosuppressive agents or their combinations with cyclophosphamide, chlorambucil, colchicine, dapsone, cyclosporine and especially azathioprine that could be used in that period for the management and treatment of complete or incomplete Behçet disease patients with or without intestinal findings, to induce rapid and durable remission of intestinal attacks before the decision of an invasive surgery (total colectomy) is made[15-21]. In other words, whether the patient is supposed to suffer from Behçet disease or IBD, the indication for surgical treatment can be made upon failure of sufficient and appropriate medical treatment or based on the severe complications such as abscess, fistula formation and iatrogenic perforation. Although systemic CSs may be useful in the early stages of severe inflammatory attacks, they are of limited value for long-term management of serious involvements whereas sustained remission can be accomplished only by the immunomodulatory agents. For instance, azathioprine or chlorambucil associated with high dose CSs should have been tried initially for the girl to obtain possible remission with long-term steroid-sparing effects. Similarly, cyclophosphamide- and cyclosporine-CS combinations have also been used between 1971 and 1989 for various symptoms of Behçet disease, even in cases resistant to conventional therapy[22-28]. Furthermore, Sanderson[29] has evaluated chronic IBD in children including Crohn's disease, ulcerative colitis, indeterminate colitis and Behçet's colitis in the review in that period and stated that treatment with drugs (sulphasalazine, steroids, azathioprine) and elemental diet are helpful and concluded that the prognosis of chronic IBD in childhood is good. More importantly, sulphasalazine with or without cyclosporine and CSs has successfully been used for the treatment of both intestinal Behçet disease and IBD[30-32].

Fourth, the authors further stated that intractable ulceration of the left foot surprisingly disappeared postoperatively after total colectomy within two weeks with no relapse of pyoderma gangrenosum for 10 years afterwards, suggesting a close relationship between pyoderma gangrenosum and intestinal Behçet disease. I do not agree with the authors on this regard and I believe that if the patient had really had Behçet disease, pyoderma gangrenosum or any other kind of cutaneous manifestations might have developed in its due course as the disease is known to be most active during the second and third decades of life. Indeed, the authors further stated in their paper that pyoderma gangrenosum might respond to surgical resection of the associated diseases, such as ulcerative colitis and Crohn's disease (see discussion section, second paragraph), and then stated in the following sentences that pyoderma gangrenosum in the present case rapidly improved after total colectomy. I agree on this regard and fortunately, total colectomy results in cure of IBD with reasonable long-term benefit in many cases. Therefore, both the authors' statements in their paper and the literature again indicate that the girl had an IBD with or without Behçet disease.

Although aphthous punched-out ulcerations may be found in about one-tenth of Behçet disease patients, they occur most frequently in the terminal ileum and cecum[33] and this finding alone is still not sufficient for the diagnosis of Behçet disease as the case should strictly fulfill the whole systemic diagnostic criteria as stated above and aphthae in the colon may be seen not only in Behçet disease, but also, for instance, in Crohn's disease[34]. Moreover, a very recent study has demonstrated that none of the clinical parameters of a total of 162 consecutive adult patients with diagnosis of IBD consisting of Crohn's disease and ulcerative colitis fulfill the Behçet disease diagnostic criteria[35]. In other words, Behçet disease was diagnosed in none of the patients even though they had various symptoms such as intestinal involvement, pyoderma gangrenosum, articular disease, skin lesions, and oral ulcer with or without HLA-B51 positivity. Furthermore, such case reports with identical and perplexing clinical presentations as compared to those of Nakamura *et al*, are still present in the literature, describing association of both diseases[32,36,37].

In conclusion, although I agree that the gastrointestinal and systemic features of Behçet disease and IBD overlap to a considerable extent that need addressing both in terms of increasing our understanding of pathogenesis and improving therapy, they are generally viewed as two distinct diseases, and oral aphthous ulcerations, genital ulcerations, papulopustular lesions or pyoderma gangrenosum on the leg with or without pathergy test positivity are all encountered findings during the course of IBD. In addition, constellation of findings for the diagnosis of Behçet disease is applicable only in the absence of other clinical explanations such as IBD. Therefore, the absence of sufficient symptoms to diagnose this young girl as "complete" or "definitive" Behçet disease

along with the presence of active colitis and ulcerations involving the entire alimentary tract, mainly colon in that case, reaching up to the terminal ileum associated with a rapid disappearance of intractable foot ulceration after surgery with the lack of demonstrated thrombotic or leukocytoclastic vasculitis (typical hallmark of Behçet disease) on colonic histopathological examination in the presented case, strongly indicates a diagnosis of pyoderma gangrenosum associated with IBD characterized by Behçet disease-like clinical presentation[38-40]. Consequently, I suggest that the authors of the present case perform HLA analysis in their patient. If it reveals HLA-B51 positivity, then the very unusual diagnosis of classified or unclassified IBD associated with Behçet disease can be made in that case. If it reveals HLA-B27 positivity, then the patient can be classified in that case as HLAB-27 positive IBD. Even if the patient is still to be accepted as having intestinal Behçet disease, it seems that the rules for the treatment of such an involvement have not been followed before the surgery.

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