Comment to "Deep vein thrombosis induced by vasculitis in the Behçet's syndrome"

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To the Editor: We read with interest the case reported by Chen and Guan[1] about a 37-year-old male with a 5-year history of Behçet's syndrome (BS) complicated by deep vein thrombosis (DVT) for 2 months. The patient developed upper abdominal pain after his warfarin was discontinued for 7 days and urgent abdominal computed tomography revealed multiple microstones in the left kidney and no other abnormality was detected. His symptoms recurred the following morning with chest pain, dyspnea, and cardiac arrest, and he was declared dead after 1 hour of resuscitation.

This article, however, raised the following comments and concerns as far as anticoagulants and immunosuppressive therapy in BS patients and gastrointestinal involvement induced by BS:

First, BS is a systemic vasculitis of unknown etiology that involves the skin, mucosa, joints, eyes, vascular, nervous system and the gastrointestinal system. Ocular, vascular, neurological and gastrointestinal involvement may associate with a poor prognosis.[2] DVT is thought to result from inflammation-related rather than hypercoagulability. Although a meta-analysis of the 3 retrospective studies indicated that adding anticoagulants to immunosuppressives did not decrease the relapse risk, no recommendation against anticoagulant use can be made because of the lack of prospective controlled trial.[3] Since almost all BS patients with aneurysms have a history of DVT, great attention should be paid to bleeding in anticoagulated BS patients complicated by aneurysms. Therefore, anticoagulation may be considered in refractory to reduce the pulmonary embolism risk, once aneurysms are ruled out.

The authors stated that no revisited guidelines about the treatment of BS were made. However, the 2018 update of the EULAR recommendations for the management of BS has been published in March 2018.[3] Another shortcoming of the report is that the patient did not receive further tests to exclude the coexistent arterial aneurysms and the patient may die from pulmonary artery aneurysms rupture rather than pulmonary embolism. Additionally, we consider that warfarin should not be discontinued for gastrointestinal endoscopy in the described patient complained of refractory venous thrombosis.

Second, rapid immunosuppressive treatment during acute attacks are the main principles in the treatment of BS. Immunosuppressives have been shown to reduce relapse rate of venous thrombosis when compared to solo anticoagulants. According to the updated guideline, glucocorticoids and immunosuppressives such as azathioprine, cyclophosphamide or cyclosporine A are recommended for the management of acute DVT in BS. There were no data to guide the management of patients with refractory venous thrombosis. Monoclonal anti-TNF antibodies could be considered in the above patients since beneficial results have been obtained in BS patients with refractory arterial involvement.[3]

In the initial treatment, the described patient was sensitive to immunosuppressive therapy, while his symptoms deteriorated rapidly on his 7th day in the hospital, which proved that the immunosuppressive therapy mentioned above was not enough. According to the updated guideline, monoclonal anti-TNF antibodies may be considered in the above patient with refractory venous thrombosis. However, there was no data about the preference of one immunosuppressive was superior to another, therefore, further clinical studies should be performed.

Third, the most frequent sites of gastrointestinal involvement of BS (GIBS) are the colon and the ileocecal region, and the reported frequency of GIBD shows wide variation (3–60%).[4] Perforation and massive bleeding are more common in GIBS due to vasculitis of BS. During acute exacerbations, glucocorticoids should be considered to promote the rapid healing of ulcers, together with 5-aminosalicylate (5-ASA) or azathioprine, and monoclonal

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anti-TNF antibodies and/or thalidomide should be considered in refractory patients. A cohort study of GIBS showed that almost a third of these patients required emergency surgery due to perforation, major bleeding.[5] Timely recognition of these complications is very important since they may be fatal if left untreated.

In this case report, we highly suspect the patient had also suffered from GIBS and 5-ASA or azathioprine should be considered, instead of only indomethacin administered per rectum therapy. If the symptoms of the patient are not relieved, urgent surgery should be considered. In addition, Budd–Chiari syndrome (BCS) cannot be completely excluded.

In summary, this interesting case aroused our attention on the anticoagulants and immunosuppressive therapy in BS patients and the management of gastrointestinal involvement. BS is a rare disease and is frequently underdiagnosed condition. Therefore, the prospective controlled clinical trials are of considerable importance.

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Conflicts of interest

None.

References

1. Chen Y, Guan JL. Is warfarin indicated in Behcet's syndrome associated with thrombosis? reflections on treatment and death of a patient. Chin Med J (Engl) 2018;131:105–106. doi: 10.4103/0366-6999.221282.
2. Esatoglu SN, Kutlubay Z, Ucar D, Hatemi I, Uygunoglu U, Siva A, et al. Behcet's syndrome: providing integrated care. J Multidiscip Healthc 2017;10:309–319. doi: 10.2147/JMDH.S93681.
3. Hatemi G, Christensen R, Bang D, Bodaghi B, Celik AF, Fortune F, et al. 2018 update of the EULAR recommendations for the management of Behcet's syndrome. Ann Rheum Dis 2018;77:808–818. doi: 10.1136/annrheumdis-2018-213225.
4. Lopalco G, Rigante D, Venerito V, Fabiani C, Franceschini R, Barone M, et al. Update on the medical management of gastrointestinal Behcet's disease. Mediators Inflamm 2017;2017:1460491. doi: 10.1155/2017/1460491.
5. Hatemi I, Esatoglu SN, Hatemi G, Erzin Y, Yazici H, Celik AF. Characteristics, treatment, and long-term outcome of gastrointestinal involvement in Behcet's syndrome: a strobe-compliant observational study from a dedicated multidisciplinary center. Medicine (Baltimore) 2016;95:e3348. doi: 10.1097/MD.0000000000003348.

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Reply to "Comment to Deep vein thrombosis induced by vasculitis in the Behçet's syndrome"

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We appreciate the attention from all the authors of the manuscript entitled "Comment to Deep Vein Thrombosis Induced by Vasculitis in The Behçet's Syndrome". As Behcet's disease belong to one type of vacuities, there is no need to repeat the term as "Vasculitis in The Behçet's Syndrome" and this type of thrombosis is regarded as inflammation related thrombosis, so inflammation is the mechanism, while vasculitis is a diagnostic term, so I recommend of change into Deep Vein Thrombosis Induced by vascular inflammation in patients with Behçet's Syndrome.

For their concerns No. 1:Authors presented background knowledge on vascular Behcet's disease (BD). However, I cannot see what is their concern related to the case. I assumed they worried about this case accompanied by aneurysms? Our enrolled 923 patients with BD who presented to our hospital with adequate medical histories and proper vascular screening exams. The raw incidence rate of vascular BD was 17.98% (166/923), Aneurysm or pseudoaneurysm was diagnosed in 1.84% (17/923) patients, mostly in male patients ($P < 0.05$, OR: 3.221, 95% CI: 1.097 to 9.112). For this case we reported, as we did not write, he was ruled out of aneurysm according to our checkup. And for a certain period, as clearly displayed in the article, he had taken the warfarin before administrated in our institution. Our case reported published in Jan. 2018, while updated EULAR for the management of BD published at the same time, why there is "shortcoming"? As mentioned in EULAR on management of vascular BD with anticoagulation, "there are no controlled data on, or evidence of benefit from uncontrolled experience with anticoagulants, antiplatelet or antifibrinolytic agents in the management of deep vein thrombosis or for the use of anticoagulation for the arterial lesions of BD". And our understanding for this guide is: It is controversial to apply anticoagulants, since lack of evidence, some experts support of application while others not. Form this case experience, (and also cases we reported and haven't reported), we kind of transferring ideal aim on anti-inflammation to both anti-inflammation and stress on anticoagulant.

EULAR states that "the venous thrombi in BD adhere to the vessel wall and do not result in emboli. Pulmonary embolism is rare despite a high frequency of venous thrombosis. Thus anticoagulants, antiplatelet or antifibrinolytic agents are not recommended". And our understanding is: It should consider the individual situation when facing a patient. To focus on individualization, obviously venous thrombi are ranging from slight to serve. For sure a doctor needs to judge the benefit and risk of treatment. "Pulmonary embolism is rare due to venous thrombosis" we don't agree with this statement of EULAR. Facing to this case reported, he had thrombosis (complete occlusion) in both legs and an elevated D-dimer. Pulmonary embolism should be cautious.

EULAR states that "Another reason to avoid these agents is the possibility of a coexisting pulmonary arterial aneurysm, which might result in fatal bleeding. The previously quoted abstract showed that anticoagulants did not reduce the risk of recurrent venous thrombosis. Controlled trials are needed". And our understanding is: It reminds the indication and contraindication. And again, lack of data. And we are working on it by this case present, and hopefully more in the future.

We reported another case, of young age, with risk of thrombosis including: hyperlipidemia, and low high density lipoprotein, mild thrombi in the limb, but developed very fast into stroke, although with enough anti-inflammatory disease. Reference to the article from Chen *et al*[1] And we also have reported on BD with Aneurysm.[2] We quite stressed on manages the complicated BD cases with multidisciplinary diagnosis and management. Some experience from Cardiology could

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be referred in thrombi cases. And it's obviously of value. Because, although with vasculitis, or aging issue, both of primary thrombi or BD with vascular thrombi shared part of the same inflammation pathway though.

Although with controversial, form those cases, we collected experience of giving more attention on treating thrombi, and prevention of its progressing. We didn't neglect the importance of baseline management for BD, and we don't want to overtreatment on thrombosis. We kind of hold the novo ideal that anticoagulation needs to be stressed in the circumstance. EULAR or other guidelines gave us great insights into BD management. This doesn't prevent clinical physicians to collect experiences and data, and develop novo ideals. Actually it clearly stated self-limitation, and encouraged further researches.

The 2nd concern of the authors is: However, there was no data about the preference of one immunosuppressive was superior to another, therefore, further clinical studies should be performed. The 3rd concern is on gastrointestinal involvement of BD. Most of the BD patients underwent enteroscope, and this patient rules out of intestinal involvement. And the patient received adequate DMARDs, clinical manifestations suggests enough treatment on inflammation reaction.

We do not have any comments on authors' 2nd, 3rd concerns and summary, as there is no new ideal. Both the statements and summary are correct but ordinary in today's knowledge.

Conflicts of interest

None.

References

1. Chen Y, Lu F, Guan JL. Progression of Behcet's disease with brain involvement: a case report (in Chinese). J Southern Med Univ 2016;36:1737. doi: 10.3969/j.issn.1673-4254.2016.12.26.
2. Chen Y, Cui JS, Cai JF, Zou J, Yazici H, Guan JL. Surgical intervention for Behcet's disease with aorta aneurysm and pseudoaneurysm: opposite outcomes in two cases. Chin Med J 2017;130:2503–05. doi: 10.4103/0366_6999.216414.

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