CASE REPORT

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Relapsing Superficial Thrombophlebitis Attacks Following Inactive COVID-19 Vaccination (Sinovac/CoronaVac) in a Previously Inactive Patient with Behçet Disease

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ABSTRACT To report a case with relapsing superficial thrombophlebitis attacks following two doses of inactive coronavirus disease-2019 (COVID-19) vaccination (Sinovac/CoronaVac) in a previously inactive young patient with Behçet disease. A 26-year-old patient with recurrent oral aphthae, erythema nodosum, and positive pathergy test was diagnosed with Behçet disease. The patient had 2 doses of SARS-Cov-2 vaccine (Sinovac/CoronaVac-China) vaccination for COVID-19 repeated each 4-week interval and he developed an attack of superficial thrombophlebitis of the vena saphena magna, proved by venous doppler ultrasound. He was treated with 4-week course of methylprednisolone (0.5 mg/kg/day) plus acetylsalicylic acid (100 mg/day) in addition to the current immunosuppressive management. A prompt and sustained response was obtained with repeated Remicade® (infliximab) infusions (5-mg/kg; weeks 0, 2, 6 and 10).

Keywords: Behçet syndrome; CoronaVac; COVID-19; infliximab; thromboembolism

Behçet's disease (BD) is a systemic inflammatory vasculitis characterized by recurrent orogenital ulcers, skin lesions, and uveitis with multiple system involvements.[1] There is a tendency to thrombosis associated with vascular inflammation in BD and venous thromboembolism is also a cause of morbidity and mortality in coronavirus disease-2019 (COVID-19) patients, resulting in thrombosis after COVID-19 vaccination.[2,3] For this reason, Sinovac/CoronaVac (China), an inactivated vaccine, is safer. We aimed to present a patient who developed recurrent thrombophlebitis attacks after two doses of inactivated COVID-19 vaccination.

CASE REPORT

In our case report, informed consent form was obtained from the case. A 26-year-old medical doctor presented to the dermatology outpatient clinic with redness, pain and a palpable nodule on the anterior surface of the left tibia, indicating erythema nodosum. A biopsy sample from the lesion and pathological evaluation revealed vascular thrombus in a medium-sized vessel, chronic inflammation in the vessel wall and mild chronic panniculitis. The patient had recurrent oral aphthae more than 3 times a year with a positive pathergy test. Other laboratory findings revealed expected results, which led to the diagnosis of BD according to the International Criteria for Behçet's Disease (ICBD). For the ICBD, ocular lesions, oral aphthosis and genital aphthosis are each assigned 2 points, while skin lesions, central nervous system involvement and vascular manifestations 1 point each. The pathergy test, when used, was assigned 1 point. A patient scoring ≥4 points is classified as having BD.[4] The patient was treated with indomethacin 25 mg twice a day, but did not respond. Azathioprine (50 mg 3 times a day) and colchicine (0.5 mg twice a day) were initiated. The patient showed clinical remission for 15 months. The patient had 2 doses of Sinovac/CoronaVac vaccine for

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COVID-19 at 4-week interval. Two weeks later, he had a superficial thrombophlebitis attack of the vena saphena magna, proved by venous doppler ultrasound (USG).

VENOUS DOPPLER USG RESULTS

1st venous ultrasonographic findings are: venous doppler USG during the first thromboembolism attack on the left lower extremity revealed a segmental increase in the vascular wall thickness and echogenicity about 3 cm distal to the vena saphena magna in the medial part of the ankle whit no lumen flow and no response to compression, indicating thrombophlebitis.

2nd venous ultrasonographic findings are: Two months after the first thromboembolism attack, the second venous doppler USG of the right upper extremity revealed chronic subacute thrombophlebitis and edema in the surrounding soft tissue of the cephalic vein branch at the 10 cm segment of the right middle forearm.

3rd venous ultrasonographic findings are: Two months later from the second thromboembolism attack, the third venous doppler USG of the right lower extremity demonstrated heterogeneous hypoechoic acute venous thrombosis in the middle medial part of the right cruris with obliteration of the vessel lumen of the vena saphena magna, which was not responding to compression. Adjacent skin and subcutaneous tissues were edematous, indicating acute thrombophlebitis.

He was treated with a 4-week course of methylprednisolone (0.5 mg/kg/day) plus acetylsalicylic acid (100 mg a day) in addition to the current immunosuppressive management. The patient responded to this regimen initially, but developed 2 more superficial thrombophlebitis attacks at every attempt for tapering the corticosteroid dose (Figure 1). A prompt and sustained response was obtained only with repeated Remicade® (infliximab) (Merck Sharp Dohme Ilaçlari Ltd. Şti., ABD) infusions (5-mg/kg; weeks 0, 2, 6 and 10).

DISCUSSION

Both arteries and veins may be affected in BD and superficial thrombophlebitis is the most common vascular finding.[1] Vascular narrowing, aneurysm, and thrombus due to perivascular and endovascular inflammation are seen in about 15% to 30% of patients. Vascular involvement is more common in men, and thrombophilic factors alone cannot explain the tendency to thrombosis.[2]

FIGURE 1: One of the superficial thrombophlebitis attacks of the patient.

Severe inflammatory response during the attacks disrupts the coagulation cascade, stimulated by cytokine storm, resulting in the ground for microvascular thrombus formation via monocyte-macrophage cells and vascular endothelial cells.[2,3,5] It has been demonstrated that the increase in interleukin-6, a proinflammatory cytokine, is related to the level of fibrinogen that supports the relationship between inflammation and procoagulant factors.[6,7] Venous thromboembolism is a significant cause of morbidity and mortality in COVID-19 patients, both in hospitalized patients and intensive care units. While the incidence of venous thromboembolism in patients with COVID-19 is up to 8% in wards, and between 16-35% in intensive care units (Table 1). This rate was reported as 58% in postmortem autopsies performed on patients who died due to COVID-19.[8]

Inactivated viral vaccines, including Sinovac/CoronaVac, are considered safe with minimal neurological adverse effect.[9] COVID-19 vaccines, in general, can cause thromboembolic events including cerebral venous thrombosis (CVT), and mRNA-based vaccines may cause pericarditis especially in younger patients following the second vaccination dose. During the early covid vaccination process, multiple cases of venous thromboembolism, particularly CVT, were seen in The Oxford/AstraZeneca (ChAdOx1-S [recombinant] vaccine) (England) re-

TABLE 1: COVID-19 vaccine and thrombosis relationship.[11]

Vaccine type	Total sample (n=69)	Alive (n=45)	Dead (n=24)
1 dose of Pfizer/BioNTech (BNT162b2) vaccine	2	2	0
2 doses of Pfizer/BioNTech (BNT162b2) vaccine	2	2	0
1 dose of Janssen (Ad26.COV2.S) vaccine	12	9	3
2 doses of Moderna (mRNA-1273) vaccine	1	0	1
1 dose of AstraZeneca (ChAdOx1 nCoV-19) vaccine	51	31	20
2 doses of name not specified	1	1	0
Time to event diagnosis	9.45±7.52	10.4±8.14	7.67±5.95

cipients, which received comprehensive media coverage and led to vaccine hesitancy. Six cases of CVT were reported in women when the Janssen vaccine (Janssen-ABD) was introduced. This has been attributed to the adenoviral vector vaccines, which induce CVT in susceptible patients. As of January 2021, 213 post-covid vaccine CVT cases have been reported globally by the European Medicines Agency, 187 reported following AstraZeneca, 25 after Pfizer, and one after Moderna. Later, CVT case series were reported in only four young and healthy patients after the Sinopharm and Sinovac/CoronaVac vaccine.[10] This is the first report of recurrent superficial thrombophlebitis after Sinovac/CoronaVac in a previously inactive young patient with Behçet disease.

Given the relapsing course of the disease in the present case and his younger age, infliximab infusion at doses of 5 mg/kg may immediately be initiated without any delay since sustained remission of vasculitic attacks could not be obtained by combination therapy of azathioprine, colchicine, and methylprednisolone. On the other hand, infliximab resulted in the cessation of relapsing thromboembolism attacks.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

All authors contributed equally while this study preparing.

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