

A Lady with Painful Nodules on Her Legs

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CASE SUMMARY

History

An 18-year-old lady presented with recurrent painful nodules over her legs for one and a half year. The lesions came in crops affecting different parts of her legs and healed with scarring. The rest of the body was not involved. She also complained of recurrent epigastric pain for one year. At the age of 15, she had history of pulmonary tuberculosis with treatment completed. There were no chest or urinary symptoms, no recent weight loss or constitutional upset. There was no history of recurrent oral or genital ulcers, history of deep vein thrombosis or other thrombo-embolic phenomenon. She was a non-smoker and non-drinker. She has never been pregnant. She did not take oral contraceptive pills. The family history was unremarkable.

Physical examination

Tender erythematous subcutaneous nodules over both shins and calves were noted (Figure 1). Some older lesions healed with post-inflammatory hyperpigmentation and scarring. The nodules were not arranged in a linear fashion and there was no subcutaneous cord palpable. There was no evidence of ankle oedema, livedo reticularis or deep vein thrombosis. Lymphadenopathy was not detected. Examination of the abdomen revealed no epigastric mass or hepatosplenomegaly. The respiratory system, cardiovascular system and the breasts were normal.

Differential diagnosis

The differential diagnoses included erythema induratum, erythema nodosum or other panniculitides such as lupus profundus. Cutaneous vasculitis like

cutaneous polyarteritis nodosa and superficial migratory thrombophlebitis were considered as well.

Investigations

The complete blood picture, liver and renal function tests were normal. Immune markers like ANF, RF, C3, C4 and ANCA were all negative. The clotting profile was normal and VDRL was non-reactive. Chest X-ray was normal. An incisional skin biopsy for histopathology and direct immunofluorescence was performed on her right leg which showed unremarkable epidermis and dermis. In the subcutaneous tissue septum, there was an inflamed and thrombosed vein with mixed cellular infiltrates of polymorphs, lymphocytes and histiocytes in the vessel wall. There was minimal spillage of the inflammatory process to the surrounding lobules. The fat lobules were viable. There was no tuberculoid granuloma. Direct immunofluorescence showed non-specific granular IgM and C3 deposit along the dermo-epidermal junction. Staining for IgG, IgA and fibrin were negative. The histological features were consistent with superficial thrombophlebitis (Figures 2 and 3).

Progress

The patient was admitted to hospital for further investigations. Screening by the gynaecologist and ENT



Figure 1: Several erythematous subcutaneous nodules over the right leg

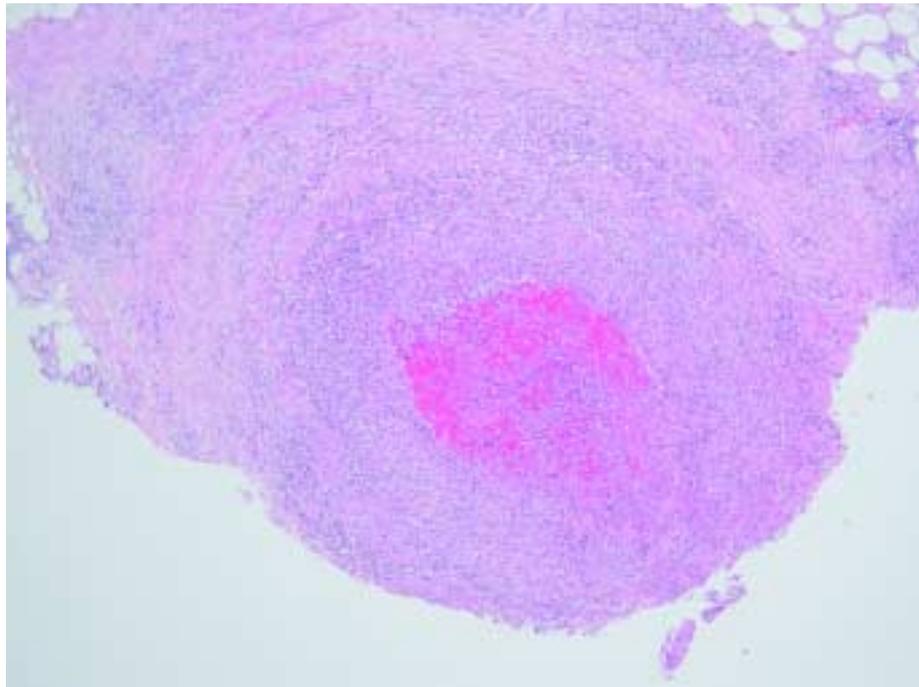


Figure 2: There is intraluminal thrombus formation in a large subcutaneous vascular structure with inflamed muscular wall. Note the relative sparing of surrounding tissue in the upper field. (By courtesy of Dr. K. C. Lee, Department of Pathology, QEH)

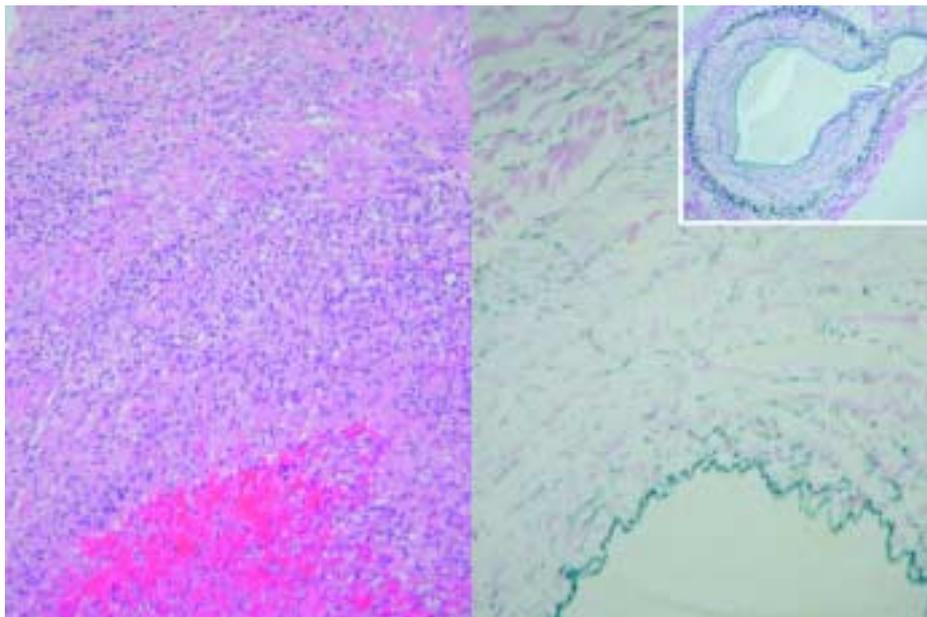


Figure 3: (Left) Please note again the luminal thrombosis and the presence of lymphocytes and histiocyte infiltration in the wall of the vessel. (Right) This is the same field as that on the left with elastic stain. Note a thin but complete internal elastic layer and most importantly incomplete concentric elastic tissue inside the muscle coat. (Insert) A subcutaneous vein of lower leg under elastic stain. Note again the prominent complete internal elastic layer, concentric rings of elastic tissue in muscle coat and the presence of a valve. (By courtesy of Dr. K. C. Lee, Department of Pathology, QEH)

surgeon were unremarkable. CEA and AFP were normal. There was no occult blood detected in the stool. No abnormalities were detected in the following tests, including doppler ultrasonogram of the legs, oesophago-gastro-duodenoscopy, barium enema and computerized tomogram scan of the abdomen. Further investigations for a possible hypercoagulable state including lupus anticoagulant screening, anti-thrombin III, protein C were all normal. The level of protein S was initially found to be low, 57% (normal: 65-140%). But with subsequent recheck it was confirmed to be normal by haematopathologist. She was closely followed up to look out for subsequent development of occult malignancies.

REVIEW ON SUPERFICIAL MIGRATORY THROMBOPHLEBITIS (SMT)

Clinical features

SMT is classified under the group of septal panniculitides with vasculitis. The typical signs are erythematous, tender subcutaneous nodules arranged in a linear fashion with a cord-like thickening of the subcutis along the involved vein. They are usually located on the lower limbs but involvement of the arms and the abdomen have also been reported. Characteristically, the location of the nodules changes from one day to another as multiple segments of the vein may be involved and hence the condition is termed "migratory".¹

Differential diagnosis

The differential diagnoses of SMT include erythema nodosum, erythema induratum and other panniculitis. Vasculitis, for example, cutaneous polyarteritis nodosa, sarcoidal granulomas, bacterial or fungal septic thrombophlebitis and lymphangitis have to be considered.

Aetiology

This form of septal panniculitis usually occurs without any documented underlying disease. It is most frequently a complication of varicose veins. The condition may develop from either a primary or secondary hypercoagulable state.² Hypercoagulable state is any condition that promotes excessive coagulation within the vascular system. A primary

hypercoagulable state is due to a specific defect in the constituents of coagulation, fibrinolysis, or both. Deficiencies of factor XII, anti-thrombin III, heparin cofactor II, protein C and protein S as well as disorder of t-plasminogen activator, dysfibrinogenaemia, lupus anticoagulant and anticardiolipin antibody syndrome may produce a primary hypercoagulable state that leads to SMT.³ Clinical indicators that suggest a primary hypercoagulable state include a family history of thrombosis, recurrent thrombosis without an apparent precipitating factor, thrombosis at an unusual site, thrombosis at an early age, and resistance to conventional antithrombotic therapy.³ A secondary hypercoagulable state may occur under the following conditions: malignancy, pregnancy, consumption of oral contraceptives, infusion of prothrombin complex concentrate, Behcet's disease and thromboangiitis obliterans.

Histopathology

Histopathologically, the lesion is centered around a large vein in the subcutis, usually in the septal region. The affected vein has a thick wall with the smooth muscle distributed in fascicles in the wall. The thrombus often completely occludes the lumen. An inflammatory infiltrate extends between the muscle bundles and a short distance into the tissue surrounding the vein. The infiltrate is composed of many neutrophils in early lesions, but later it consists mainly of lymphocytes, macrophages, and a few giant cells. Granulomas with giant cells can be found within the wall or within the lumen of the affected vessel if recanalization of the vein takes place.

SMT and malignancy

The main concern of SMT is the paraneoplastic character. Isolated vein thrombophlebitis is uncommonly associated with internal malignant disease whereas multiple and migratory lesions are much more often paraneoplastic. When the diagnosis of SMT is made, the patient should be examined and investigated carefully to detect any underlying occult malignant disease or hypercoagulable state.

In 1865, Trousseau described an association between SMT and malignancy. The incidence of thrombotic episodes in patients with malignancy ranges from 5% to 15%. The thrombotic rate for pancreatic carcinoma may be as high as 50%. SMT is also

associated with neoplasms of the stomach, prostate, lung, liver, bowel, gallbladder, ovary, lymphoma and leukaemia.⁴ The resulting hypercoagulable state may also lead to deep vein thrombosis and pulmonary embolism. The occult tumours are mostly detected within two years from the development of SMT but the delay can be as long as 55 to 68 months. The exact underlying mechanism is not fully known but it is said that neoplastic cells can activate coagulation directly by activation of platelets or by production of procoagulants such as prothrombin activators via the stimulation of monocytes and macrophages. Moreover, the tumour cells can directly produce procoagulants.

Mondor's disease and Trousseau's syndrome are two famous conditions of SMT associated with malignancies. Mondor's disease was first described in 1939. It is the presence of thrombophlebitis of the anterior chest wall presenting as palpable tender or nontender cords. It may be associated with primary or recurrent breast cancer, breast abscess, breast augmentation or reduction mammoplasty. The underlying condition is, however, usually benign. Although women between the ages of 21 and 55 years are most frequently affected, men comprise approximately one third of the reported cases.⁴

Treatment

Detection and treatment of the underlying disease, if present, is of utmost importance. Malignancy should be ruled out. The hypercoagulable state may show

improvement after treatment of the underlying malignancy. It may be resistant to warfarin and heparin may be needed. Unfortunately, this is frequently complicated by haemorrhage into the tumour. Treatment of cutaneous lesions is otherwise conservative. Exercise is a good prophylaxis. Stocking and bandage in the involved leg is helpful in acute episodes. Non-steroidal anti-inflammatory drugs may be used when necessary. In chronic and recurrent cases, especially those associated with malignancy, heparin and fibrinolytic drugs may be used.¹

Learning points:

Patients with SMT should be thoroughly investigated to rule out underlying malignancies and hypercoagulable states.

References

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