Unusual coexistence of Stewart-Treves syndrome and sickle cell anaemia: a case of dual pathology

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SUMMARY

Chronic lymphoedema can rarely be complicated by an angiosarcoma. This combination called Stewart-Treves syndrome usually observed in upper limb in patients of post-mastectomy with axillary lymph node resection. Here, we report a male patient who had a 10-year history of right leg elephantiasis. Later on, he developed two large ulceronodular masses in the same leg with few satellite nodules in the surrounding skin. With the clinical suspicion of malignancy, a wedge biopsy was performed which revealed histological features of angiosarcoma with sickled red cells. The above knee amputation specimen received further confirmed the histological diagnosis. The investigation for haemoglobinopathy also suggested the presence of sickle cell trait. This report describes a multifocal tumour as a rare manifestation of Stewart-Treves syndrome in a post-filariasis case with sickle cell trait, which is an extremely uncommon combination.

BACKGROUND

The development of angiosarcoma in the setting of chronic lymphoedema is known in patients with breast carcinoma.[1] The upper limbs are susceptible to lymphoedema in women post-mastectomy with axillary lymph node dissection.[2] Stewart-Treves syndrome (STS) is characterised by angiosarcoma that manifests in the setting of chronic lymphoedema. Even though it was first described in the background of lymphoedema as a sequel of radical mastectomies,[1] it was also observed in patients with filariasis and idiopathic lymphoedema, which were considered to be its rare causes. Being extremely rare, only about 400 cases have been reported worldwide, and 90% of which occupy the upper limb as a sequel of lymphoedema post-mastectomy.[3] The authors here report an unusual case of STS of lower limb that developed in a patient with chronic idiopathic lymphoedema secondary to filariasis.

CASE PRESENTATION

A young man had lymphoedema of the right leg following filarial infection about 10 years ago for which he was treated with diethylcarbamazine, 400 mg two times per day for a period of 2 years in addition to antibiotics. He then presented to the surgery outpatient department with exophytic growths on the right lower leg associated with pain of few months' duration. On local examination, his right leg showed extensive skin thickening in the setting of chronic lymphoedema with two ulceroproliferative growths each measuring 7×6×3.4 cm on the anterior aspect of the right leg (shin). The growths were soft to firm, ulcerated with everted margins having raw surface oozing of blood. The adjacent skin also revealed multiple small nodules of average size 1.5×1 cm, few being ulcerated. An ipsilateral inguinal lymphadenopathy was noticed as two lymph nodes, each measuring 1.5×1.5 cm, were firm, mobile and non-tender. The systemic examination was unremarkable.

INVESTIGATIONS

Routine laboratory investigations did not reveal any abnormality. The patient was Hepatitis B surface Antigen (HBsAg), Hepatitis C virus (HCV), HIV and COVID-19 negative. Aspiration cytology of the right inguinal lymph node revealed features of reactive lymphadenitis without any evidence of any live or dead microfilariae. Radio-imaging of the head, neck, chest and abdomen was within normal limits. With the clinical suspicion of a malignant tumour, a wedge biopsy specimen was received consisting of two soft to firm, greyish-white to reddish skin-covered tissues measuring 2×0.6×0.5 cm and 1×0.5×0.4 cm. H&E-stained sections showed epidermis, dermis and deeper tissue. The epidermis revealed focal ulceration and inflammatory exudate. The dermis and deeper tissue showed a tumour comprising of irregular fascicles and bundles of spindle-shaped cells (figure 1). At places, the tumour exhibits anastomosing vascular channels lined by plump to epithelioid cells protruding into the lumen. These cells display nucleomegaly pleomorphism with coarse chromatin and prominent nucleoli in some areas (figure 2A). Mitotic activity was brisk (figure 2B). The tumour cells also revealed intracytoplasmic lumina having red

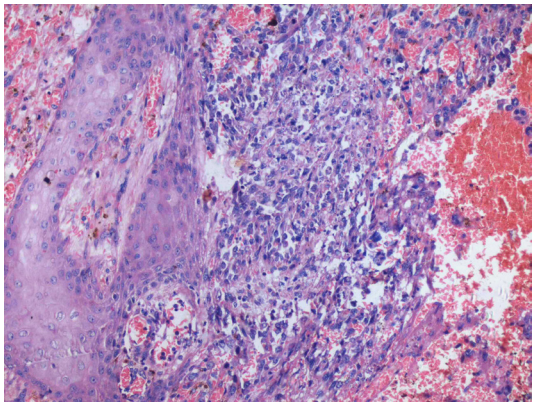

Figure 1 Section shows ulcerated skin and the underlying tumour comprising of cellular and haemorrhagic areas. The cellular zones display bundles and fascicles of oval to spindle cells (H&E; 10×).

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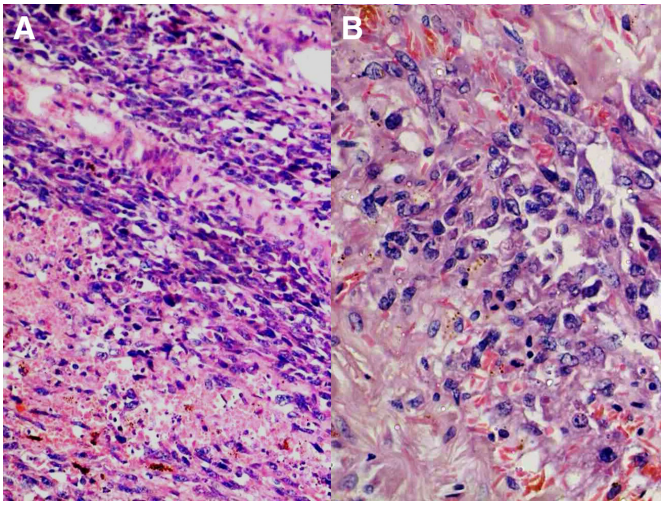

Figure 2 (A) The cells have scant amount of pale cytoplasm, enlarged pleomorphic nuclei with coarse chromatin and prominent nucleolus. At places, these cells are lining the vascular spaces (H&E; 20×). (B) Bizarre nuclei, mitotic figures are also evident (H&E; 40×).

blood cell in some. The vascular channels and tumour cells were seen dissecting the surrounding fibrocollagenous stroma, with lymphoid infiltrates and haemorrhage. The diagnosis of malignant vascular tumour favouring angiosarcoma of the right leg was offered. Subsequently, an above knee-amputated resection specimen of the lower limb was received for histopathological examination (figure 3). Both the tumour masses and satellite nodules revealed similar morphology. In addition to this, the tissue examined also revealed large areas of haemorrhage and many sicked red cells in areas of congestion (figure 4). The resection margins were uninvolved by the tumour. The histology confirmed the biopsy diagnosis of angiosarcoma in the setting of chronic lymphoedema. Immunohistochemistry performed further confirmed the vascular nature as the tumour displayed endothelial markers CD31 as distinct membranous positivity (figure 5).

OUTCOME AND FOLLOW-UP

The patient was followed up after surgical management almost every 6 months. Until the time of his last follow-up early this year, the patient was alive; however, he was unable to perform his regular work after surgery (farming as his profession). He mentioned that he could manage routine daily activities.

Figure 3 The resection specimen of amputated lower limb. Tumour masses are ulceronodular growths of size 5×5 cm with multiple small satellite nodules in the adjacent area. The entire skin of the limb was thickened, oedematous, dry and rough favouring elephantiasis (gross).

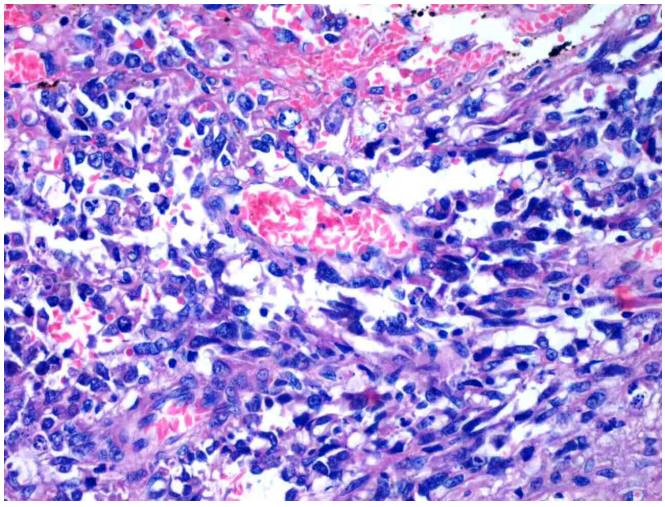

Figure 4 The tumour displays large areas of haemorrhage and congestion, which are packed with sickled red blood cells (H&E; 40×).

DISCUSSION

Lymphoedema is characterised by the accumulation of protein-rich fluid in extremities that can occur due to lymphatic blockade. The factors considered to be responsible for the development of vascular oncogenesis in this setting of lymphoedema include lymph stasis impairing the local immune response by the disruption of immune cell migration and angiogenesis seen as growth of new vascular channels and collaterals. Thus, increased angiogenesis and absence of immune response against the background of lymphoedema promote the development of malignant vascular neoplasms, such as STS and Kaposi's sarcoma.[4 5] The period from lymphoedema to the appearance of the tumour may range from 1 to 26 years.[6 7] The patients with STS initially present with subcutaneous violaceous nodules or eschars which can then progress and coalesce to form indurated plaques with evidence of pitting oedema.[8] A dermoscopic examination in its early stage displays classic colour graduation of red, purple and blue, an important finding not observed in other vascular lesions; therefore, it can be used as a clinical clue for the detection of the lesion in its early phase. However, in the present case, no dermoscopic examination was performed as the patient presented with an obvious tumour in the surgical outpatient department.[9]

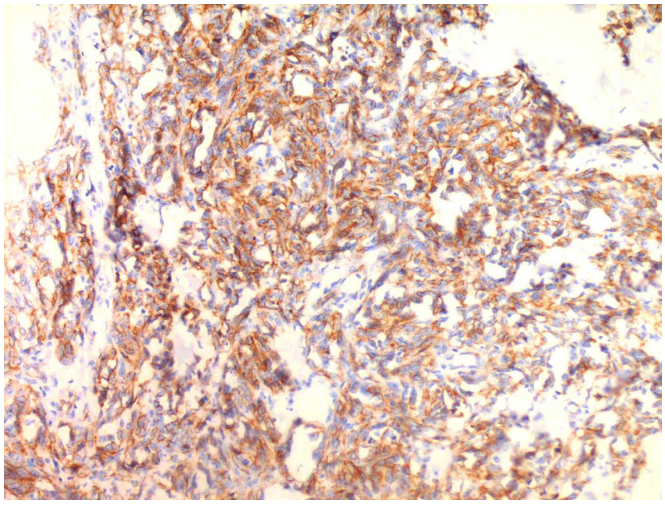

Figure 5 The tumour cells are CD31 positive. (immunohistochemistry; CD31 cytoplasmic positivity, H&E; 40×).

In advanced stages, the tumour manifests as multiple, red-blue polypoid nodules, with ulceration and necrosis complicating the late stage of the disease.[10] The closest differentials can be squamous cell carcinoma (SCC) in the setting of non-healing ulcer (Marjolijn's ulcer) and malignant melanoma (MM). Clinically, SCC presents as a large cauliflower to ulcerative growth, which arises from the skin and displays histomorphology as cohesive, irregular sheets of polygonal to round to spindle cells with moderate eosinophilic cytoplasm, hyperchromatic, pleomorphic nuclei and presence of keratinisation. In contrast, multiple lesions, satellite nodules, uninvolved skin and tumour displaying predominantly spindled morphology, focally lining vascular spaces, revealing nuclear pleomorphism, coarse chromatin, prominent nucleoli and intracytoplasmic neolumina are the features in favour of angiosarcoma. MM involves the overlying skin and reveals the presence of junctional activity. The tumour cells exhibit spindled morphology without any specific pattern; however, they showed nuclear pleomorphism with prominent nucleoli and intracytoplasmic melanin pigment. The present case did not display any of these features.[11] Both SCC and MM are known for early lymph node metastasis, while enlarged inguinal lymph nodes in the present case revealed features of reactive lymphadenitis. The literature quotes that there is no consensus regarding optimal management strategy for angiosarcoma developed in the context of STS. Some sarcoma centres however advocate a radical resection of the limb involving forequarter or hindquarter amputation.[8] A chemotherapy regimen like paclitaxel has been used as a palliative measure in inoperable cases. Regardless of treatment modality, the overall prognosis of STS is poor, with high rate of local recurrence and metastasis.[4 12] Invariably, most patients with STS die from metastatic disease within 2 years.[4 10] Although the prevalence of sickle cell trait in India and in central India is 1%–40% and 22.5%–44.4%, respectively, this presentation is unique as there is no such case reported in literature addressing the coexistence of this dual pathology.[13]

Patient's perspective

I was suffering from filariasis of right leg since few years for which I took medications around 2 years. This disease has caused swelling along with thick and dry skin of my right lower leg to which I got used to. After around 8 to 10 years, I noticed small nodule on my right leg, which I ignored even though it was increasing in size. After few months another nodule developed in its adjacent part. To my surprise, it got ulcerated and the pain was unbearable. Therefore, I consulted my local doctor who referred me to higher medical centre. I made up my mind and went Nagpur for further consultation where I was diagnosed of a tumour. To know the exact nature, doctor removed a small portion of it and sent to laboratory. I was asked to review with biopsy report after 8–10 days. I returned to my village with a satisfaction that doctor is taking due care of my problem. After 2 weeks I collected my biopsy report and consulted my surgeon. After going through the report, he called my family members and explained us the nature of my disease. However, I was not able to understand the disease much as I was uneducated. The doctor further explained to me that the treatment for this type of cancer is amputation of my leg. This news about my disease and getting aware about its treatment was shocking to me as well as my family. I was completely broken down as I was the only earning member of my family. It took few months to make up the mind of my entire family for this devastating kind of operation. The doctor assured me about my well-being once the tumour along with leg is completely removed. He also consoled me that my life span quality of life will be better if I will use artificial limb, he also promised for helping me out for the same. Being a government hospital, which have free schemes for cancer patient, I got operated. My entire amputated right leg was then sent to laboratory for complete diagnosis. I recovered completely after surgery and was sent back home after a week. The special tests were also done on my tumour which confirmed that I got a sarcoma of blood vessel which I possibly have developed due to swollen foot which was due to Filaria. On further investigation, I was also known to have a disease of blood called Sickle cell anaemia, which runs in family. I was not advised any kind of further treatment, but was asked to come for follow-up every 6 monthly. Initially visits to hospital were regular later on I lost interest. Because of money constraints I could not go ahead with artificial limb prosthesis. In spite of all odd things happened to me, I still pray to God that I am all alive even though with disability and I am also thankful to my doctor - a god in human being for saving my life.

The patient himself has contributed the patient's perspective and the same was translated and transcribed by the authors.

Learning points

- Knowledge and high index of suspicion can help to recognise Stewart-Treves syndrome in its early phase as it mimics a spectrum of conditions ranging from non-healing ulcer to malignancy.
- This rare entity should be considered in the list of differentials while dealing with a case of multiple, ulceronodular lesions in the setting of chronic lymphoedema.
- The patients with chronic lymphoedema should undergo long-term follow-up so that lesions can be picked up in its initial stage of development as early diagnosis is crucial for prompt management, to reduce morbidity and improve patients' survival.
- The discovery of sickle cell anaemia, a rare occurrence, was an incidental finding not reported in the literature to date.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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