

Cytodiagnosis of Angiosarcoma following Radical Mastectomy: A Rare Case Report of Stewart-Treves Syndrome

SANDHYA BISWAL¹, RANJANA GIRI², MOULI MISHRA³, SUBRAT KUMAR SAHU⁴, PRAJNA DAS⁵

ABSTRACT

Stewart-Treves Syndrome (STS) is a rare, highly aggressive cutaneous angiosarcoma with poor prognosis. It develops in a background of chronic lymphoedema, most commonly following mastectomy and adjuvant radiotherapy for carcinoma of the breast. The condition is uncommon, with the literature largely limited to isolated case reports and small case series. Radiotherapy is believed to increase the risk of STS by inducing tissue fibrosis, lymphatic obstruction, and persistent lymphoedema. Chronic lymphoedema results in local immune dysfunction, creating a microenvironment conducive to malignant transformation and oncogenesis. We report the case of a 52-year-old woman who developed STS involving the right upper limb seven years after undergoing radical mastectomy followed by postoperative adjuvant chemoradiotherapy for breast carcinoma, right-side. She presented with progressive swelling of the affected limb followed by multiple purplish cutaneous nodules two months later. On clinical examination, the nodules were immobile, firm to hard in consistency, tender, and measured between 0.5 cm and 2 cm in diameter. Positron Emission Tomography-Computed Tomography (PET-CT) scan showed post Modified Radical Mastectomy (MRM) status with multiple subcutaneous nodules on right limb and no other distant metastasis. Fine-Needle Aspiration Cytology (FNAC) revealed features suggestive of a malignant neoplasm. Subsequent histopathological examination, supported by Immunohistochemical (IHC) analysis, confirmed the diagnosis of high-grade angiosarcoma overlying lymphoedema. This case highlights the diagnostic value of FNAC as a rapid and minimally invasive initial investigative tool in post-mastectomy patients with chronic lymphoedema who develop suspicious cutaneous lesions. Early recognition and prompt diagnosis are crucial to improving clinical outcomes in this rare but fatal condition.

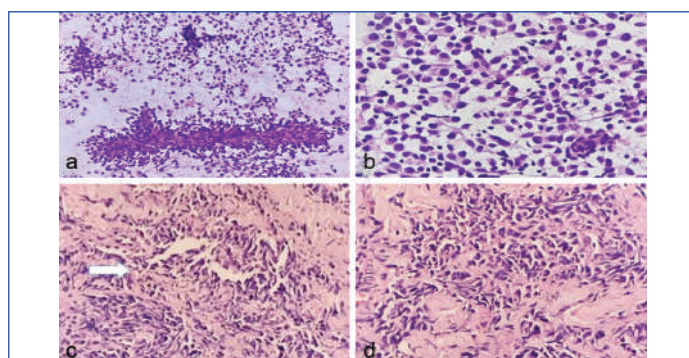
Keywords: Chemoradiotherapy, FNAC, IHC, Lymphoedema, Oncogenesis

CASE REPORT

A 52-year-old female came with diffuse swelling with multiple nodular lesions in the right limb for two months. She had undergone Modified Radical Mastectomy (MRM) nine years ago for carcinoma breast and had received postoperative neoadjuvant chemoradiotherapy. After seven years of surgery, the patient developed gross swelling of right limb followed by cutaneous nodules two months later. On examination, there were multiple firm to hard and tender purplish swellings with largest measuring 2 cm in diameter over a diffuse swelling of right hand [Table/Fig-1a,b]. There was no local rise in temperature. FNAC yielded yellow coloured particulate material. Cytosmears were highly cellular showing discohesive clusters, sheets and scattered malignant cells in a necroinflammatory background. Many cells were present surrounding vascular channels [Table/Fig-2a,b]. These cells were pleomorphic with irregular nuclear margin, coarse chromatin and few with prominent nucleoli. With these findings, a differential diagnosis of secondary angiosarcoma developing over lymphoedema and metastatic carcinomatous deposits in a known case of carcinoma breast (post-MRM) was made. Patient consulted the oncosurgery department for further evaluation where whole body PET-CT scan was advised which revealed post-MRM status with multiple subcutaneous nodules on right limb and no other distant metastasis. Her haematological parameters like haemoglobin, total leucocyte count and total platelet count along with biochemical parameters like Liver Function Tests (LFT) and Renal Function Tests (RFT) were within normal limits. Core biopsy of the nodule was sent to Pathology department. Biopsy revealed a tumour in which pleomorphic tumour cells were arranged in solid sheets, cords and at places lining the interconnected vascular channels [Table/Fig-2c,d]. The cells were spindled to polygonal having hyperchromatic nuclei and scanty cytoplasm. The histopathological diagnosis was angiosarcoma with differential diagnosis of metastatic carcinoma in a follow-up case of carcinoma of breast. IHC was done which

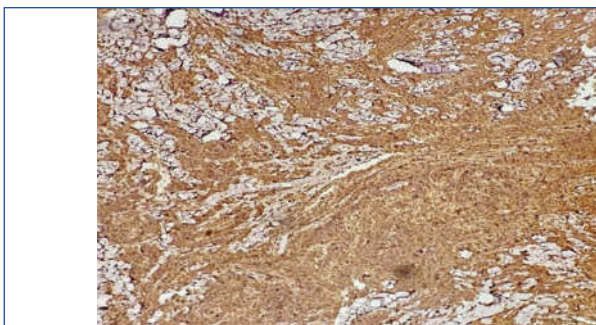


[Table/Fig-1]: a) Diffuse swelling of right hand; b) Multiple purplish hard nodules.

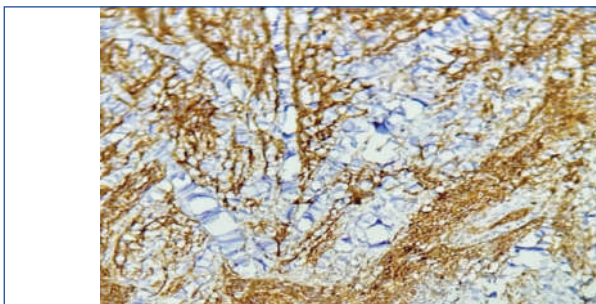


[Table/Fig-2]: a) (H&E, 200x)- Cytosmear shows pleomorphic tumour cells in loosely cohesive clusters, in perivascular areas and scattered singly in necrotic background; b) (H&E, 400x)-Cytosmear shows scattered oval to spindled tumour cells with hyperchromatic nuclei and scanty to moderate cytoplasm; c,d) (H&E, 400x): Biopsy showing pleomorphic tumour cells around interconnected vascular channels.

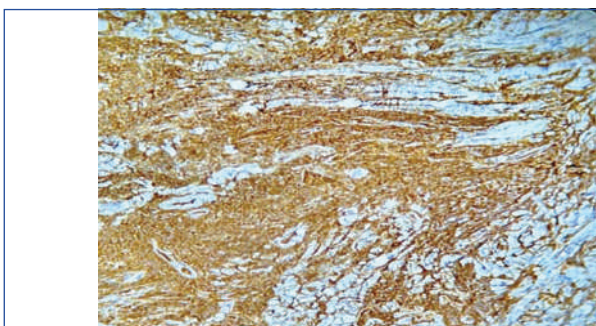
revealed the tumour cells were positive for Vimentin, CD 31, CD 34 and factor VIII [Table/Fig-3-6] and negative for CK, ER and GATA-3 [Table/Fig-7-9]. The diagnosis of malignant mesenchymal tumour, suggestive of angiosarcoma was given. Amputation of right limb was done and sent for histopathological examination. Biopsy of the amputated specimen revealed an infiltrating tumour where atypical looking pleomorphic endothelial cells lining the interconnected



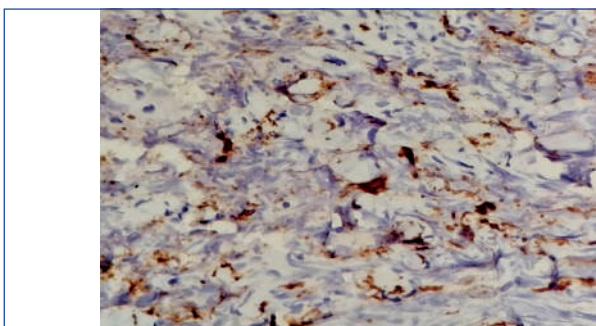
[Table/Fig-3]: IHC of Vimentin (200x)- Diffuse positive in tumour.



[Table/Fig-4]: IHC of CD 31 (200x)-Diffuse positive in tumour cells.



[Table/Fig-5]: IHC of CD 34 (200x)-Diffuse positive in tumour cells.

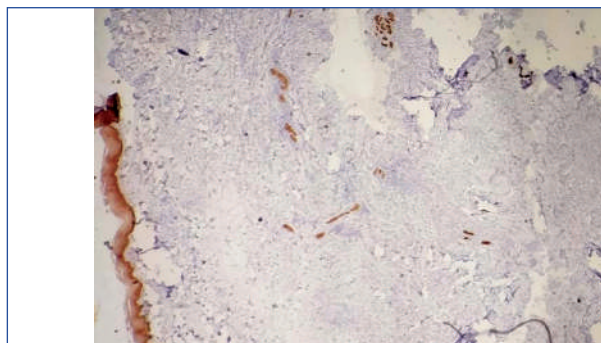


[Table/Fig-6]: IHC of factor VIII (400x)-diffuse positive in tumour.

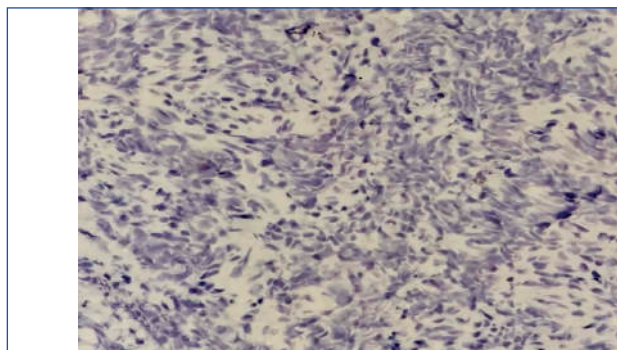
vascular channels with entrapment of dermal appendages and extending to subcutis were seen [Table/Fig-2c,d]. Numerous mitotic figures (52/10 HPF) and extensive areas of necrosis were noted. Finally, diagnosis of angiosarcoma with lymphoedema was made. It was a case of STS as the angiosarcoma developed after longstanding lymphoedema following adjuvant chemoradiotherapy for postoperative carcinoma breast. After amputation, the patient took radiotherapy for four months and died later.

DISCUSSION

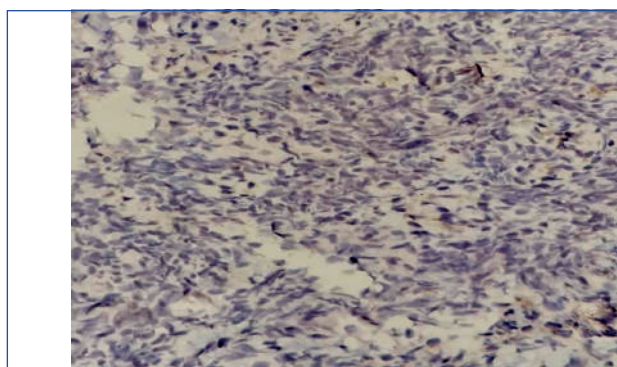
Lymphangiosarcoma or STS is a rare skin angiosarcoma with grave prognosis [1]. It was first described in 1948 in a series of six cases of lymphangiosarcoma after post mastectomy with chronic lymphoedema by Dr. Fred W. Stewart, Professor of Pathology, and Dr. Norman Treves, Associate Professor of Surgery, both from Cornell University Medical College, New York, USA [2]. Roy P et al., (2004) reported five STS cases, with disease-free survival in four patients following forequarter amputation; one declined surgery and received isolated limb perfusion



[Table/Fig-7]: IHC of CK (200x)- Tumour cells showing negative expression, arrows showing positive internal control in epithelium.



[Table/Fig-8]: IHC of GATA3 (200x)- Negative expression in tumour.



[Table/Fig-9]: IHC of ER (200x)- Negative expression in tumour cells.

[3]. McKeown DG and Boland PJ (2013) described STS 15 years post-breast cancer treated with doxorubicin, resulting in death within 18 months [4]. Farzaliyev F et al., (2020) reported two cases treated with radical excision and Hyperthermic Isolated Limb Perfusion (HILP) using TNF- α and high-dose melphalan, achieving complete pathological response only with neoadjuvant therapy [5].

The STS has a rapid progression with strong propensity for distant metastasis. To date, over 400 cases have been documented in literature [6]. Its incidence in patients who survive for at least five years post radical mastectomy ranges from 0.7% to 0.45% [7]. Overall, it constitutes approximately 2% of all sarcomas [8]. Cutaneous lymphangiosarcomas account for around 5% of all angiosarcomas and predominantly arising in limbs following chronic lymphoedema [9].

The early clinical presentation of STS is often subtle, making differentiation from other dermatological conditions challenging. Inadequate clinical history can lead to misdiagnosis. Elderly females are affected commonly, correlating with the peak incidence of breast cancer, typically occurring between 65 and 70 years of age [10]. The disease frequently manifests as multifocal lesions, usually emerging after a prolonged period (9-11 years) of chronic lymphoedema in the upper extremity, often following breast cancer surgery with axillary lymph node dissection and adjuvant radiotherapy [11,12]. Clinically, STS presents as rapidly expanding purplish red macules with surrounding induration, predominantly on the arm, forearm, or hand [13].

The exact pathogenesis of STS is currently unclear, though several hypotheses have been postulated. Research suggests that systemic carcinogenic factors, combined with neoplastic cell transportation within edematous tissue as collateral circulation following radiation therapy, may contribute to its development [7]. Out of multiple risk factors, the most important cause of STS is congenital or acquired chronic lymphoedema [14]. Radiotherapy contributes indirectly to an increased risk by causing axillary-node sclerosis resulting in lymphatic blockade and lymphoedema [15]. Ruocco V et al., postulated that chronic lymphoedema induces a localised state of immunodeficiency, further predisposing to malignant transformation [16]. Another theory suggests that lymphoedema results in the accumulation of protein-rich interstitial fluid and growth factors leading to abnormal lymphangiogenesis and subsequent malignant transformation [17].

In 1959, McConnel EM and Haslam P postulated three stages of STS: i) prolonged lymphoedema leading to fat and collagen degeneration, especially in the reticular dermis; ii) premalignant phase characterised by lymphangiomatosis with foci of proliferative endothelial lining presenting as superficial bruises or vesicles, and deeper areas of induration and haemorrhage; iii) malignant transformation into lymphangiosarcoma [18].

The differential diagnosis of STS includes: a) haemangioma; b) Kaposi sarcoma; c) cutaneous telangiectatic metastatic breast disease [14]. Haemangioma is a benign vascular neoplasm. In capillary haemangioma, there is a nodular aggregates of small capillaries with endothelial proliferation whereas in cavernous haemangioma, there is thin-walled dilated congested capillary proliferation with scanty stroma [19]. Kaposi sarcoma is a malignant vascular tumour of intermediate grade where the patient also presents with reddish purple maculo-nodular lesions. It is associated with HIV infection. Histopathology reveals dilated to slit like proliferation of vascular channels lined by atypical endothelial cells; in later nodular phase there is proliferation of spindle cells in fascicles having mild nuclear atypia with interspersed thin walled capillaries. The tumour cells are positive for HHV8, CD31, CD34 and negative for S100, Desmin, SMA and CK [20]. Cutaneous telangiectatic metastatic breast disease is a type of metastatic breast cancer where the cancer cells spread to skin, presenting as visible dilated blood vessels (telangiectasia) on the skin surface, typically appearing as red, patchy areas or nodules. But histopathology differentiates it from STS [21].

Adverse prognostic factors include the presence of metastasis at the time of diagnosis, deep or visceral involvement, tumour size exceeding 5 cm, tumour necrosis, and absence of surgical excision [15]. Conversely favourable prognostic factors include age below 50 years, tumour localisation on the trunk rather than the extremities and lower stage [7]. Despite advancements in therapy, there is no standardised treatment for STS, and its overall mortality rate remains exceedingly high [15]. Close clinical monitoring, often necessitating admission to a telemetry or intensive care unit, is imperative for these patients [22].

CONCLUSION(S)

A high-index of clinical suspicion for lymphangiosarcoma should be kept in mind in patients with chronic lymphoedema following radical mastectomy and adjuvant chemoradiotherapy. FNAC can facilitate early detection, while histopathology and immunohistochemistry remain the gold standards for definitive diagnosis. Due to aggressive nature of STS, characterised by frequent local recurrences with high metastatic potential, a multidisciplinary approach is paramount for optimising early detection, intervention, and overall patient management.

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