

**Stewart-Treves Syndrome Associated with False-positive Serological Tests of Syphilis:
Possible Relation with the Tissue Coagulation Factors**

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ABSTRACT

Stewart-Treves syndrome (STS) is defined as a lymphangiosarcoma in a setting of postmastectomy upper extremity lymphedema. On the other hand, positivity of nontreponemal and treponemal syphilis tests can occur in some healthy conditions and diseases besides syphilis. Here we report a case of chronic lymphedema that progressed to STS in a 68-year old woman with a previous subtotal mastectomy, associated axillar lymph node dissection, chemotherapy and radiotherapy. The patient also had false-positive syphilis tests, and increased tissue coagulation factors and products. Our report aims to explain the possible relationship between the false-positive syphilis tests and the coagulant factors, and the potential facilitating role of these factors triggering the formation of precipitants and ultimately the development of the malignancy.

Keywords: Blood coagulation tests, false positive reactions, rapid plasma reagin, Stewart Treves syndrome, Syphili *Treponema pallidum* particle agglutination

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INTRODUCTION

STS has been described by Stewart and Treves as a lymphangiosarcoma, which appears in the upper extremity lymphedema following postmastectomy. Though the majority of STS cases reported the association with this special condition, a few cases have been reported after chronic lymphedema due to other causes such as congenital, post-traumatic and filarial lymphedema (1). On the other hand, it has been stated that in the development of lymphedema-related tumors, the newly formed collateral vessels that can produce an environment rich in growth factors may play a role in addition to the immunosuppression within the skin (2).

CASE REPORT

Here, we described a 68-year-old woman who complained for 5 months of progressive swelling, severe pain and gradual increase in the number of bruise-like spots on the right arm. The patient was diagnosed with breast carcinoma (a mix of an invasive ductal and invasive micropapillary carcinoma), and underwent right subtotal mastectomy and axillary lymph node dissection eleven years ago. Post-operatively, the patient received both chemotherapy and radiotherapy. There was no history of post-operative complication, infection, trauma or thrombosis. The patient subsequently developed lymphedema of the ipsilateral arm six years following the surgery and it gradually increased in volume. Ten and a half years after the surgery, the patient had a massively swollen right arm and multiple cutaneous bruise-like spots.

On the dermatological examination, the patient's right arm and forearm were swollen, and had a well-circumscribed nodule on the skin of the right forearm that had a purplish discoloration and was ulcerated (Figure 1). There were also multiple small plaques around the nodule which resembled the color of the big nodule. The rest of the dermatological examination was normal. On the physical examination of the patient, only one big epitochlear

lymphadenomegaly (1 cm in size) on the right elbow was detected. The clinical examination of the other systems including respiratory, gastrointestinal, genito-urinary, and central nervous system did not show any pathology. In the laboratory tests, a high erythrocyte sedimentation rate (ESR) and moderate elevation of C reactive protein (CRP) were detected as 54 mm/hr and 13.46 mg/L respectively. D-dimer level was 710 ng/ml (Reference range: 0-550 ng/ml) and fibrinogen level was 650mg/dl (Reference range: 200-400 mg/dl). Prothrombin time was reduced (9.5 seconds) and prothrombin activity (PTA) was increased to 145.5% (Reference range: 70-130%). Syphilis serum rapid plasma reagin (RPR) and *Treponema pallidum* particle agglutination (TPPA) test titers were positive at 1:320 and 1:160 respectively as well.

Except for the high CA 15-3 level (125.50 U/ml [Reference range: 0.01-32.4 U/ml]), the other tumor markers (AFP, CEA, CA 19-9 and CA 125) were within the normal limits. The soft tissue ultrasonography showed a solid, non-capsulated, plenty vascularized soft tissue masses with irregular borders. No additional pathology was detected in the other laboratory tests (including complete blood count, pregnancy test, rheumatoid factor, antinuclear antibody, anti-ds DNA and anti-ss DNA, hepatitis B and C tests, HIV tests, anti-borrelia IgM and IgG, serum protein electrophoresis, wound swab for both cytopathological examination and bacteriological/viral cultures), arterial and venous Doppler-ultrasonography of the right arm, chest radiography, echocardiography and abdominopelvic ultrasonography.

There was no evidence of syphilis in the patient's husband and other family members, and the patient clearly denied having extramarital sexual behaviors, and blood transfusions. Fluorescent treponema antibody-absorption (FTA-ABS) IgG and IgM examinations, which were performed for the purpose of verifying of the tests, were negative. The big nodular lesion on the forearm was biopsied with deep excision, and histopathological examination demonstrated a tumor consisting of spindle cells, and vessels deformed by atypical and pleomorphic endothelial cells which were on the background of dense fibrous stroma (Figure

2a,b). The vessels did not have any erythrocytes and positively reacted with D2-40 immunohistochemistry (Figure 2c). The atypical tumor cells reacted strongly with Ki-67 (Figure 2d). The lesion did not invade underlying subcutaneous fatty tissue or muscle. These findings were consistent with the diagnosis of a lymphangiosarcoma.

After the diagnosis, the right arm of the patient was amputated, and additionally she received adjuvant chemotherapy. The patient also underwent oral anticoagulant therapy with warfarin sodium (5mg/day). Two months after the amputation, the RPR and TPPA tests, and the coagulation tests were repeated. Each of the nontreponemal test titers was $< 1:8$, and was considered nonreactive. The results of the coagulation tests returned to the normal values. The patient is still alive in the postoperative fifth month, and still continues to receive the anticoagulant therapy. No new lesion emerged in nearby areas of amputation site or ipsilateral breast.

DISCUSSION

In the STS, these sarcomas appear to be more consistent with hemangiosarcomas than the lymphangiosarcomas. The distinction between the two types is slim, especially as the origin of the cells in both is endothelial. The incidence of STS is estimated to be 0.45% in patients still alive 5 years after radical mastectomy. In approximately 90% of cases, the tumor was reported to be in the upper limb. The pathogenesis of STS is unknown. Schreiber et al. postulated that local immunodeficiency could be a causative factor, as the “immunologically privileged site” allows sarcomatous degeneration in the edematous region to go unnoticed by the immune system.

Typically, the tumor is a bluish, slightly raised macule or plaque on a lymphedematous extremity. These lesions tend to grow, coalesce, ulcerate and spread proximally and distally to

involve the entire arm. The disease tends to metastasize through the blood to distant organs as well (1). Both the lesions of our patient and progression of the disease process were compatible with the literature. The median time from mastectomy to the development of angiosarcoma is 10 years, ranging from 5 years to 27 years (1). In our patient, it was 11 years. The tumors consist of vascular cavities lined with spindle-shaped endothelial cells containing large nuclei and prominent nucleoli on the background of fibrous stroma (1).

We also had similar findings. The survival of patients is low and the treatment of choice is amputation (1). On the other hand, the nontreponemal tests of syphilis may show cross-reactivities with some diseases and healthy conditions, including chickenpox, rheumatoid arthritis, pregnancy, and advanced age (3). The RPR and the venereal disease research laboratory (VDRL) tests are flocculation-based (clumping) tests. They work according to the presence of precipitation or clumping of the antigen-antibody complex. In agglutination, precipitation and flocculation reactions, an antigen-antibody recognition followed by aggregation, and this aggregate is in the form of lattice. In the nontreponemal tests, because the aggregate stays suspended, the term flocculation is used rather than agglutination to describe this type of reaction.

Generally, serum is the specimen of choice for both nontreponemal and treponemal tests, which we used as well. If plasma samples are used, the blood is collected in the specified anticoagulant in order to prevent coagulation (4). The results of the PRP and VDRL can show median sensitivities of 86% and 78%, respectively during the primary-stage, and 73% and 71%, respectively for late-stage of syphilis (3). RPR appears positive not only in syphilis (5,6), but also in other treponemal infections, and some diseases such as connective tissue diseases, malignancy, and diseases with abnormal immunoglobulin (5) and malaria (7).

Additionally, in a recent report, it has been stated that the test could be false-positive in the cases of false labor, megaloblastic anemia, aplastic anemia, redundant prepuce, congenital

malformation of heart, and salpingitis (6). Treponemal tests of syphilis such as FTA-ABS and TPPA are more specific than RPR, but false-positivity can also occur (5). The TPPA is also an agglutination-based test. However, FTA-ABS is an indirect immunofluorescent test and it is run at a standard dilution without titers. False-positive FTA-ABS test results may occur in systemic, discoid, and drug-induced varieties of lupus erythematosus due to the presence of anti-DNA antibodies (4). Although the RPR and TPPA test results were positive for our patient, syphilis was ruled out because she had no clinical manifestations of syphilis and contact history, and the FTA-ABS tests were negative. On the other hand, the possible etiological reasons that can lead to the false-positivity of these tests were also ruled out through our clinical and laboratory examinations.

The exact cause of the false-positive syphilis tests is still unknown. It has been stated that certain types of immunoglobulin with special structures, heavy molecular weight or over a certain quantity were probably the reasons for the false-positive syphilis tests (5). On the other hand, malignant tumors are often accompanied by increased risk for procoagulant activity. The level of D-dimer, which is a product of fibrinolysis increases in such diseases (8).

Also, the initiation of blood coagulation by expression and upregulation of tissue factor (TF) which is a 47-kDa transmembrane glycoprotein, and an impaired clearance of activated coagulation factors, contribute to the hypercoagulability in several malignancies including breast tumors (9). Due to the presence of high levels of D-dimer and fibrinogen, shortened PT time and increased PTA, we thought that these factors might have been responsible for the false-positivity of these precipitation based tests by increasing the tissue coagulation products, and actually leading to large amounts of precipitates. Moreover, the normalized coagulation test results and nonreactivity of syphilis tests two months after the amputation and the anticoagulant therapy, support our inferences. For these reasons, we also think that the high-level of all the precipitant factors may predispose the tissues for a second malignancy such as

STS. This predisposition could have been caused by a restricted and hypoxic environment which was surrounded and created by these precipitates. Indeed, to provide cellular adaptation to hypoxic conditions, many gene transcriptions which are controlled by “hypoxia-inducible factor” (HIF) occur (10). HIF-1 alpha subunit is stabilized by reactive oxygen species, and it provides the synthesis of many proteins including heat-stress proteins (Hsp’s) in the tissue (10,11).

By the enhancement of the Hsps, the tissue angiogenesis, which is induced by vascular endothelial growth factor (VEGF) is triggered, and continues until the desired oxygen level is achieved in the tissue (12). For the mentioned reasons, we also thought that many vascular occlusions which were formed by the precipitates, could have started a hypoxic environment, a tissue damage/degeneration, and consequently neovascularization. Ultimately, the chronicity of the process could have created a sarcomatous differentiation and proliferation in the immunosuppressed and growth factor-rich tissue. Our report is intended to give an explanation about the possible relation between the false-positive syphilis tests and the coagulant factors, and the potential facilitating role of these factors in the development of malignancy. According to our literature search, the patient is the first reported case with STS which was presented with false-positive syphilis tests.

CONCLUSION

The patient presented had both STS and positive RPR and TPPA tests. However, our laboratory examinations showed that the positivity of the syphilis tests was false-positivity. Moreover, the patient also had high levels of D-dimer and fibrinogen, shortened PT time, and increased PTA. Therefore, we thought that these factors might have been responsible for the false-positivity of the syphilis tests by increasing the tissue coagulation products. Moreover, these

factors can cause a precipitation, the precipitates can lead to a hypoxic and restricted environment, and the hypoxic region may become predisposed to the oxidative stress and tissue degeneration, and eventually cancer development. Based on the mentioned information and our findings, we recommend that these coagulation factors be followed closely during, and even many years after the treatment of primary malignancies against the possibility of secondary tumor development. And perhaps, in such patients a lifelong prophylaxis with anticoagulants may be life-saving. Additionally, if such false-positivity is not recognized in these patients, it may result in the unnecessary treatment of syphilis.

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Fig 1: Difference in the appearances of the two arms (a), The livid tumoral lesion on the edematous right arm (b), distant (c) and closer (d) views of the tumor.

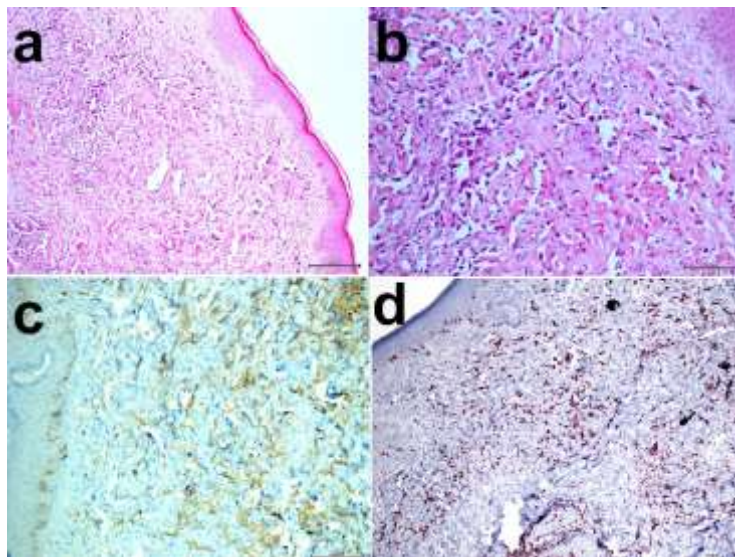


Fig 2: Histopathological and immunohistochemical views of the lesion. HEX100 (a), HEX200 (b), D240X200 (c), Ki67X100 (d).