Elevated Coagulation Factor VIII Plasma Activity in a Patient with Lymphangiosarcoma

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Abstract

A 72-year-old woman was referred to our hospital for palliative care. Fifteen years earlier, she had undergone total hysterectomy and radiotherapy for cervical cancer. One year before her referral, she visited a hospital due to a gait disturbance and was diagnosed with lymphangiosarcoma. The level of coagulation factor VIII plasma activity was >201% (normal range: 62-145%) and the immunohistochemical results were positive for factor VIII-related antigen in a tumor specimen. To the best of our knowledge, this is the first report of high coagulation factor VIII plasma activity in a patient with lymphangiosarcoma.

Key words: cervical cancer, chronic lymph edema, lymphangiosarcoma, factor VIII-related antigen

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Introduction

Lymphangiosarcoma appears as a complication of longstanding lymphoedema in the arm after mastectomy and/or radiotherapy for breast cancer and is also known as Stewart-Treves Syndrome (STS) (1). Although this type of tumor is not directly related to breast cancer or radiotherapy, a common factor is chronic lymphedema; therefore, other causes of chronic lymphedema can lead to the development of vascular sarcoma (2-4). We recently reported the case of a patient with lymphangiosarcoma as an image submission (5). Lymphangiosarcoma cells frequently express positive endothelial markers, including CD34, CD31, vimentin and coagulation factor VIII-related antigen (6, 7). Coagulation factor VIII-related antigen is a glycoprotein synthesized primarily in endothelial cells and megakaryocytes (8). This protein plays a central role in primary hemostasis by promoting adhesion of platelets to subendothelial surfaces and sites of vascular damage (9). Increased plasma concentrations of coagulation factor VIII-related antigen, a carrier for coagulation factor VIII, have been shown to occur in various medical conditions associated with increased endothelial cell proliferation and vascular damage (10). Therefore, in the present case, we investigated whether coagulation factor VIII-related antigen was expressed in the patient’s tumor cells and/or elevated in the patient’s plasma.

Case Report

A 72-year-old woman was referred to our hospital for palliative care. She had undergone total hysterectomy and radiotherapy for cervical cancer in 1995. Because her lymphoedema had progressed after treatment, she had undergone lymphaticovenous anastomosis twice; however, the lymphedema did not improve. She had observed a purple ulcerated lesion on her oedematous right thigh in 2007; however, she did not see a doctor. On admission to another hospital in 2010, she presented with significant lymphedema in her right thigh, a decreased thigh function with intense pain and a raised, swollen and ulcerated area with multifocal hemorrhagic or solid purple-coloured lesions. Lesions were also observed on her back and hips (Fig. 1). She was confined to bed. Because neither systemic chemotherapy nor immunotherapy with interleukin-2 were effective, she was referred to our hospital. She was given palliative care until
her death (5). A postmortem examination revealed tumor cells in a lymphovascular growth pattern compatible with lymphangiosarcoma. The tumor had spread to nearby organs (the lower thigh muscles and pelvic bone); however, no distant metastasis was detected. Immunohistochemistry was performed according to the modified method originally described by Pusztaszeri et al. (11). Anti-human CD31 monoclonal antibodies (clone 1A10), anti-human CD34 monoclonal antibodies (clone NU-4A1) and anti-human D2-40 monoclonal antibodies (clone D2-40) were purchased from Leica Microsystems K.K. (Tokyo, Japan), Nichirei Bioscience Inc. (Tokyo, Japan) and Covance Japan Co. Ltd. (Tokyo, Japan), respectively. The microdissected and pretreated samples were incubated with each antibody at 20°C for 60 minutes (dilution 1/100). Anti-human factor VIII-related antigen polyclonal antibodies (clone F8/86) were purchased from Dako Japan Inc. (Tokyo, Japan) and the sample was incubated with these antibodies at 20°C for 60 minutes (dilution 1/1,200). The results were negative for epithelial markers and positive for endothelial markers of CD31 and CD34. The tumor cells also expressed D2-40, a marker of lymphatic endothelium (Fig. 2). To determine the pathogenesis of this disease, we performed serological screening for human acquired immune deficiency virus (HIV), human herpes virus 8 (HHV-8) and Epstein-Barr virus (EBV). No HHV-8 DNA, EBV DNA or anti-HIV antibodies were detected. No immunoglobulin (Ig) G4-positive lymphoplasmacytic cells were observed in the specimen on immunohistochemistry. Interestingly, the level of coagulation factor VIII plasma activity, measured at Mitsubishi Chemical Medience Corporation (Tokyo, Japan), was greater than 201% (normal range: 62-145%). In addition, the immunohistochemical results were positive for coagulation factor VIII-related antigen in a tumor specimen (Fig. 3).

Discussion

In this patient, STS spread to the muscles of the lower thigh and the pelvic bone after treatment of cervical cancer and the level of plasma coagulation factor VIII-related antigen was elevated. To our knowledge, this is the first report of changes in the activity of coagulation factor VIII associ-
ated with STS.

Immunohistochemical staining for coagulation factor VIII-related antigen is used as a useful marker of endothelial cells in a variety of nevoid, reactive and malignant vascular cutaneous proliferations, although not all endothelial cells synthesize or store this molecule (11, 12). Coagulation factor VIII is highly sensitive to proteolysis and is protected by the formation of a high-affinity complex with coagulation factor VIII-related antigen that is released into the circulation. The half-life of coagulation factor VIII-related antigen bound to coagulation factor VIII is significantly longer than that of plasma coagulation factor VIII in patients lacking coagulation factor VIII-related antigen, namely, those with type 3 von Willebrand disease (13, 14). In our present case, the tumor tissue was positive for coagulation factor VIII-related antigen and the level of plasma coagulation factor VIII activity was elevated. The unusual production of coagulation factor VIII-related antigen in lymphangiosarcoma cells might prolong the half-life, and hence might increase the activity of plasma coagulation factor VIII.

STS is most frequently associated with postmastectomy lymphedema, with an estimated incidence of 0.45% in patients who live five years after radical mastectomy. Approximately 90% of reported STS cases occur in the upper limbs after mastectomy (15). Surgical resection for local disease (amputation or wide excision) is the only curable treatment (16). Radiation and chemotherapy may be useful when combined with radical surgery or in the treatment of metastatic disease (17). Nonetheless, despite treatment, the overall prognosis remains poor. When the disease is suspected, it needs to be diagnosed as early as possible.

In conclusion, we showed increases in both the plasma activity level and the tissue expression of coagulation factor VIII-related antigen in a patient with STS. Whether this phenomenon occurs in other STS cases should be examined. Conceivably, the activity of coagulation factor VIII-related antigen in plasma might be useful for differentiating this disease from common lymphoedema. Lastly, we would like to emphasize that replication of the present results by a larger number of cases is needed since this is only a single case report.

The authors state that they have no Conflict of Interest (COI).

References


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