Fatal venous embolism in a patient with advanced extramammary Paget disease

Running title: Embolism in a patient with EMPD

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Extramammary Paget disease (EMPD) is a rare intraepithelial malignancy arising in areas rich in apocrine glands such as the vulva, scrotum, penis, perianal region and axilla [1]. EMPD usually localizes in the epidermis, but it can also invade into the dermis, resulting in lymph node or distant metastases. It is well known that patients with advanced malignancies sometimes develop blood coagulation disorders including thrombosis [2, 3]. Here, we report the first case of portal and splenic vein embolism in a patient with advanced EMPD.

A 69-year-old woman was referred to us for further evaluation of a 3-year history of erythema with focal erosion on the left genital region (*figure 1A*). We diagnosed it as EMPD by a skin biopsy. We performed a wide local excision. Histopathological examination showed numerous Paget cells invading into the dermis and permeating into lymphatic vessels (*figure 1B, 1C and 1D*). Ten months after the surgery, she noticed left inguinal lymphadenopathy. A lymph node biopsy showed metastasis, but no distant metastatic lesion was found by computerized tomography (CT). We performed inguinal lymph node dissection, and 7 lymph nodes showed metastases. Three months after the lymph node dissection, metastasis in lumbar vertebrae was found. In addition, a few weeks later, she had severe abdominalgia. Abdominal ultrasound examination and CT revealed portal and splenic vein embolism, splenic infarction, ascites and hepatatrophy

(*figure 1E*). A blood coagulation test showed the abnormal levels for D-dimer (20.0 ug/mL; normal range, <1.0 ug/mL), antithrombin III (39%; 80-120%), and fibrinogen (152 mg/dL; 170-410mg/dL). Although cytological examination of the ascites did not show any neoplastic cells, the serum level of carcinoembryonic antigen (CEA) was increased (80.7 ng/mL; <5.0 ng/mL). We started chemotherapy with docetaxel and anticoagulant therapy with heparin. The abdominal pain was improved temporarily, and CEA (20.8 ng/mL) and D-dimer (12.8 ug/mL) were decreased one month after chemotherapy. However, we could not continue the chemotherapy because of her poor physical condition. Three months later, abdominal pain reoccurred, but a CT scan showed no metastatic lesion except for a bone lesion. A blood examination revealed liver dysfunction, and levels of CEA (76.8 ng/mL) and D-dimer (20.7 ug/mL) were increased again. Although we continued anticoagulant therapy, her liver function became worse and she died 4 months after recognition of the embolism. We did not perform autopsy because of her family's refusal.

Coagulation abnormalities such as Trousseau's syndrome, a brain embolism related to malignancy, sometimes occur in patients with advanced cancer [2, 3]. Various tumor-derived factors including tissue factor and mucin are related to the cause of an embolism [3]. We consider that the reason for the development of the fatal venous embolism in our

patient was a hypercoagulative state induced by tumor progression. There was no evidence of a metastatic lesion in the abdominal cavity by CT and cytological examination of the ascites, and the blood coagulation test showed abnormalities. Treatment for an embolism generally includes anticoagulation and excision of the lesion [3]. However, it is often difficult to remove the whole malignant lesion. Chemotherapy is one of the options for treatment of an embolism in patients with advanced cancer, but it can be a risk for the development of another embolism [4]. In our patient, the levels of CEA and D-dimer decreased and abdominal pain and ascites were temporarily improved after chemotherapy. Therefore, chemotherapy might have been effective for the embolism in our patient.

As far as we know, there has been no previous report of fatal embolisms in a patient with EMPD. Generally, portal and splenic vein embolisms can occur in patients with malignancies around the portal or splenic vein [5-7]. However, our patient had no metastatic lesions around the abdominal cavity. This means that advanced skin cancer can also cause portal and splenic embolisms even if the patient does not have a lesion in the abdominal cavity. Although it may be difficult to prevent and predict an embolism, if patients with advanced skin cancer have abdominal pain without any metastatic lesions in the abdominal cavity, a blood coagulation examination should be performed in addition

to CT and ultrasound examination. If a portal or splenic vein embolism is shown by those examinations, we must consider treatment with an anticoagulant and anticancer drug.

The authors declare no conflict of interest.

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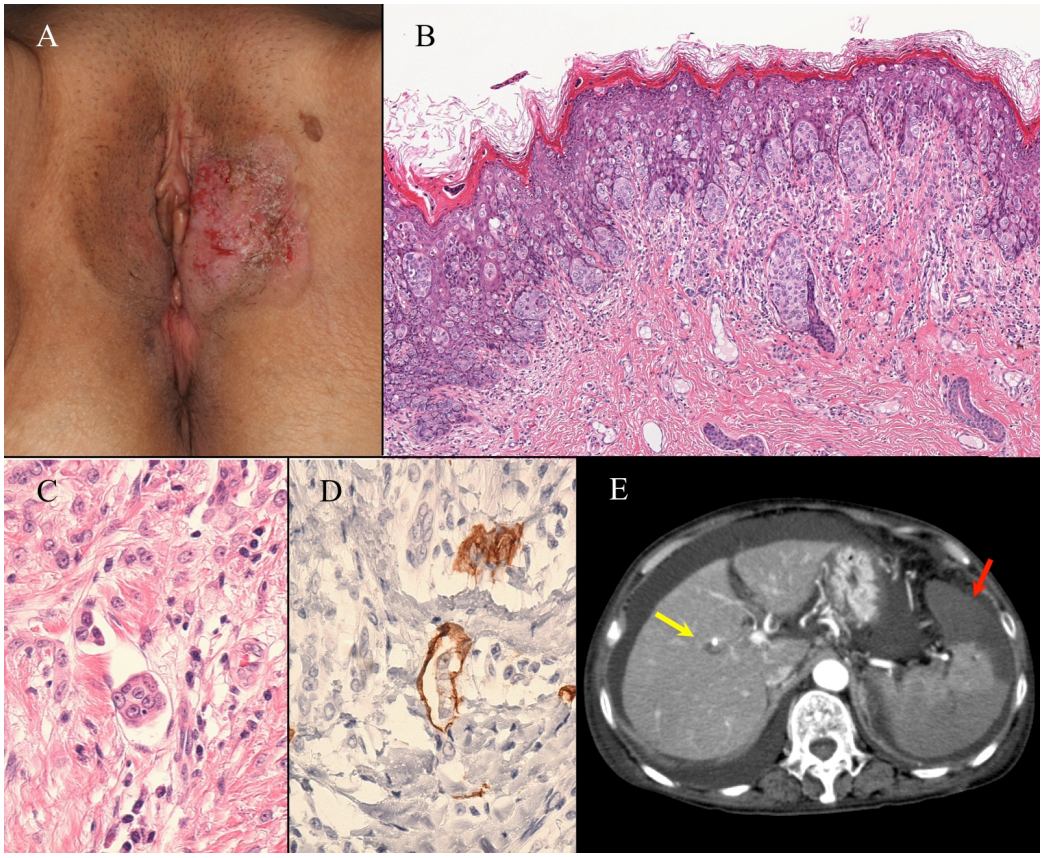
Figure legends

Figure 1. A) Physical findings. Erythema with erosion in the genital area measuring 5x5 cm. B) Histopathological findings. Paget cells in the epidermis and dermis (HE staining, x100). C) Paget cells invaded into a lymphatic vessel (HE staining, x400). D) Tumor cells in the lymphatic vessel (D2-40 staining, x400). E) CT scanning revealed a portal vein embolism (yellow arrow) and splenic infarction (red arrow).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