

## Brain metastasis from extramammary Paget's disease

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### ABSTRACT

Herein, we present a case of extramammary Paget's disease with brain metastasis that was diagnosed pathologically for the first time in Japan. Moreover, invasive extramammary Paget's disease (with distant metastasis) highly resistant to treatment. Only for brain metastasis, we may control the tumor by surgical resection and stereotactic radiosurgery (SRT) for the treatment of intracranial metastases was assessed.

An 76-year-old man was diagnosed with extramammary Paget's disease of the vulva at nearby hospital. Surgical resection and sentinel lymph node dissection were then performed, and the patient received chemotherapy because multiple lymph node metastases were suspected. The patient's response to chemotherapy was poor, and he was in the state of Progressive Disease. He complained of dyslexia and was referred to another hospital when he was 81 years old. Plain magnetic resonance imaging (MRI) was conducted, and two brain tumors in the vicinity of the left cerebellar tent were suspected.

In our hospital, gadolinium contrast-enhanced MRI was performed and showed a tumor in the cerebellum (left posterior temporal lobe) and another tumor under the tent (left cerebellar hemisphere). Significant edema was also noted. Based on these findings, the intracranial lesion was diagnosed as metastatic brain tumor. The pathological diagnosis was brain metastasis from extramammary Paget's disease. Postoperative intracranial residual disease was treated with stereotactic radiosurgery. MRI showed that the size of the cerebellar lesions decreased, and no recurrence of cerebral lesions was observed. SRT for extracranial lymph node metastases was performed.

Mass reduction and SRT may be the best way to treat brain metastasis from extramammary Paget's disease.

Keywords: brain metastasis, extramammary Paget's disease, stereotactic radiosurgery

#### Abbreviations:

CK: cytokeratin

GCDFP-15: gross cystic disease fluid protein 15

HER-2: human epidermal growth factor receptor 2

MRI: magnetic resonance imaging

PET: positron emission tomography

PET-CT: positron emission tomography-computed tomography

SRT: stereotactic radiosurgery

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Received: March 3, 2020; accepted: March 27, 2020

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## INTRODUCTION

Paget's disease can be classified into mammary Paget's disease and extramammary Paget's disease. Mammary Paget's disease is a condition in which breast cancer has progressed from the breast ducts to the epidermis. Extramammary Paget's disease is an adenocarcinoma originating from the epidermis, which is different from mammary Paget's disease. The incidence of extramammary Paget's disease in Japan is about 8%, and that of invasive extramammary Paget's disease (with distant metastasis) is only approximately 10%. In a US database, only 1,400 cases were recorded within 35 years, of which 2.5% are infiltrating cases. As the number of cases is low, guidelines for the treatment of such condition have not been established, and extramammary Paget's disease, in which the tumor is only located in the epithelium, can be treated if the whole lesion is completely removed. By contrast, invasive extramammary Paget's disease (with distant metastasis) is highly resistant to treatment, and chemotherapy (alkyl-type) is provided as an additional treatment in Japan. However, the prognosis is generally poor. Infiltration is most commonly observed in lymph node metastases, followed by lung and liver metastases. Only few reports about brain metastases with a confirmed diagnosis are available. Based on our investigation, only one case was diagnosed via radiological examination and one case was pathologically diagnosed via biopsy. A specimen must be collected to confirm the diagnosis. Furthermore, instead of biopsy, complete resection of the tumor in the left posterior temporal lobe with significant edema and the large tumor was conducted to improve symptoms and control the lesion.

Immunostaining was performed, and the specimen was found to be positive for cytokeratin (CK) 7 and gross cystic disease fluid protein (GCDFP)-15 and negative for CK20. The pathological diagnosis was extramammary Paget's disease. Stereotactic radiosurgery with Novalis was performed as a post-treatment for the excisional cavity in the cerebrum and the residual tumor in the cerebellum. Recurrence was not observed in the area where the lesion was resected, and the residual tumor decreased in size after radiation. The pathological diagnosis was then confirmed. Thus, stereotactic radiation therapy may be effective for the treatment of extramammary Paget's disease.

## CASE REPORT

### *Clinical history*

An 76-year-old male was diagnosed with an ulcer in the vulva at nearby hospital (Fig. 1). Biopsy revealed that the tumor contained Paget's cells; moreover, the patient was diagnosed with extramammary Paget's disease based on the immunostaining results (CK7: positive, CK20: negative, and GCDFP-15: positive) (Fig. 2). Then, he underwent surgical resection for the primary tumor and sentinel lymph node dissection. One year back, positron emission tomography-computed tomography (PET-CT) scan (Fig. 3) revealed multiple lymph node metastases in the para-aortic lymph nodes and inguinal lymph nodes, and chemotherapy (docetaxel course 4) was provided as post-treatment. However, the previous PET-CT scan did not reveal a lesion indicative of intracranial metastasis. He complained of dyslexia and was referred to another hospital when he was 81 years old. Magnetic resonance imaging (MRI; Fig. 4) of the head showed a brain tumor near the left cerebellum tent. Thus, the patient was referred to our hospital. Neurological examination findings showed dyslexia and omission symptoms. However, other symptoms, such as paralytic symptoms, were not observed.

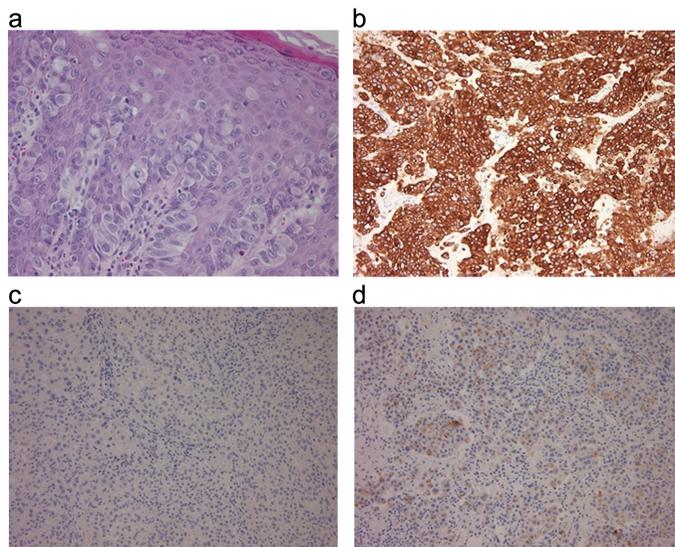
In gadolinium contrast-enhanced MRI (Fig. 5), a ring-shaped tumor was observed in the left posterior temporal lobe and another tumor was found in the left cerebellar hemisphere across the

tent. The size of the tumor in the cerebrum, which was located in the left posterior occipital lobe, was 30 mm × 40 mm, and the tumor in the cerebellum was not continuous with the cerebrum. However, it was observed in the cerebellar hemisphere. Moreover, significant edema was noted around the tumor in the cerebrum.



**Fig. 1** Image of the primary lesion

On the left side, a red ulceration is predominantly observed in the vulva. The black line marks the area for excision.



**Fig. 2** Pathological findings

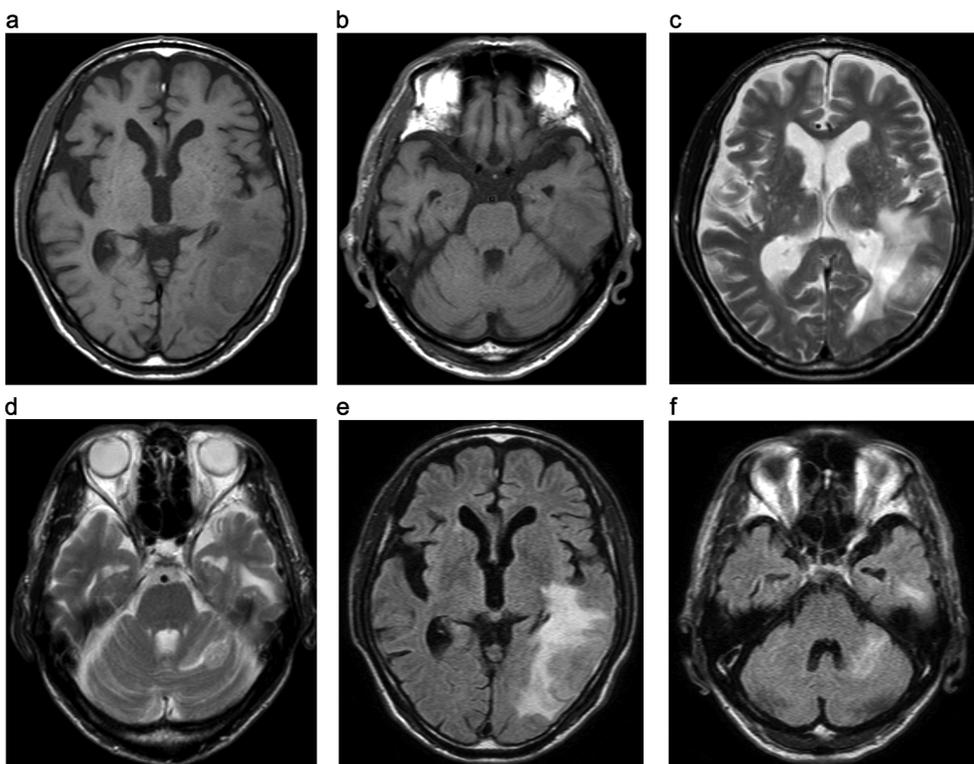
**Fig. 2a:** Isolated specimen of the primary lesion: Hematoxylin and eosin staining showed the presence of Paget cells, which are large cells with bright and abundant cytoplasm (magnification, 100×).

**Fig. 2b-2d:** Based on the immunostaining results, the specimen tested strongly positive for CK7, (c) negative for CK20, and (d) weakly positive for GCDFP-15.



**Fig. 3** Positron emission tomography

Although positron emission tomography-computed tomography scan showed hot spots indicative of metastasis in the para-aortic lymph node and inguinal lymph node, metastasis to solid organs, such as the lung and liver, was not observed.

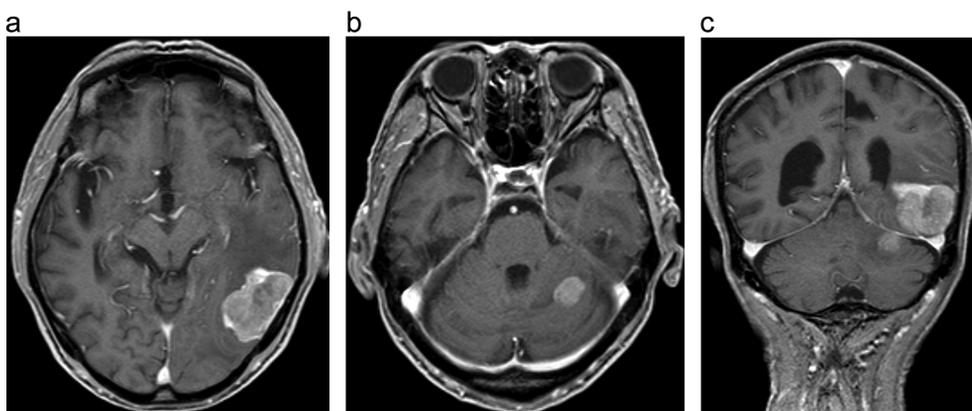


**Fig. 4** Magnetic resonance imaging

**Fig. 4a-4b:** Magnetic resonance imaging: T1-enhanced image.

**Fig. 4c-4d:** T2-enhanced image.

**Fig. 4e-4f:** Fluid attenuation inversion recovery (FLAIR) image



**Fig. 5** Gadolinium-enhanced magnetic resonance imaging  
**Fig. 5a-c:** Gadolinium-enhanced magnetic resonance imaging: T1-enhanced image.

#### *Surgery and histopathology*

Based on the clinical course, the patient was diagnosed with metastatic brain tumor.

Because the tumor was large and the surrounding edema was evident, mass reduction via craniotomy was performed for the lesion in the left posterior temporal lobe to improve the symptom and prognosis. Under general anesthesia, the head of the patient was placed in a prone position and fixed with a MAYFIELD 3-point fixed machine, and surgery was performed. In addition to the preoperative measurements, an optical navigation system (Medtronic) was used to determine the position of the tumor. The tumor was almost clearly defined visually in the normal brain. However, the boundary was not clear in some cases, indicating the possibility of invasion. Suctioning was performed. However, the tumor was fibrous and hard and could not be aspirated. The inside of the aspirator was removed using Cavitron ultrasonic surgical aspirator (CUSA, Amco), and the tumor film was moved to the inside, peeled off, and removed completely. The lesions in the cerebellum were difficult to remove via the same craniotomy area, and only reduction of the cerebral lesions and the tumor in the left posterior temporal lobe could be achieved.

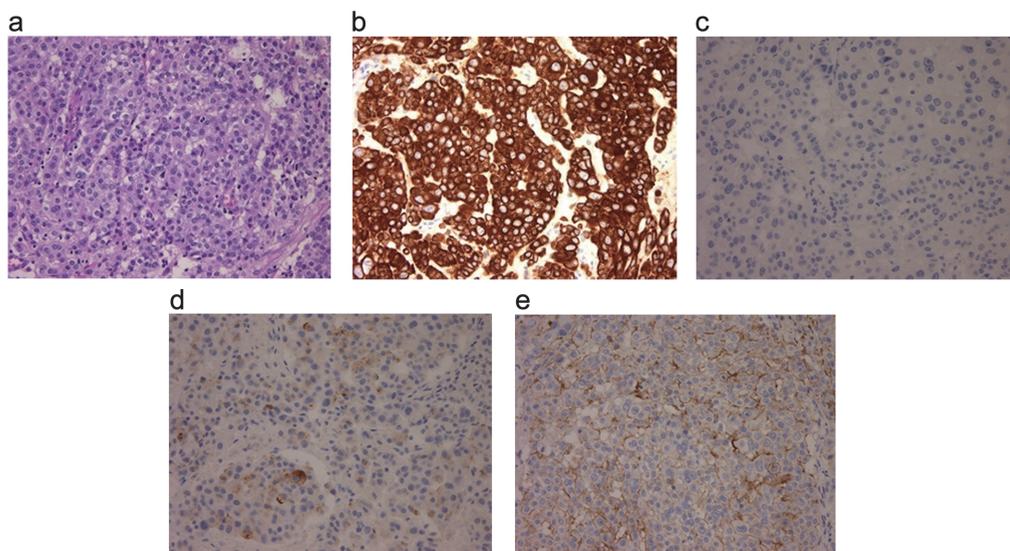
Extramammary Paget's disease was diagnosed using the surgical specimen, which was a tumor containing Paget cells, and the immunostaining result was similar to that of the primary lesion (Fig. 6). The patient was diagnosed with brain metastasis.

#### *Postoperative therapy*

The tumor in the left posterior temporal lobe could be removed completely (Fig. 7). After the treatment, the patient's condition improved, and he received stereotactic radiation therapy (39.4 Gy, five times) using Novalis (Brain Lab) for the tumors in the left posterior temporal lobe and the left cerebellar hemisphere. The size of the tumor decreased after tumor resection and radiation therapy (Fig. 8). Stereotactic radiosurgery (Novalis) was performed for extracranial multiple lymph node metastases (50 Gy, 20 times). However, it was not effective.

To assess the diameter of the tumor diameter, plain MRI was performed because the patient presented with renal failure. He developed hydronephrosis due to bilateral ureteral obstruction and lymph node enlargement.

He continued treatment. However, hydronephrosis did not improve, and the patient presented with renal failure and died of acute respiratory failure associated with flooding.



**Fig. 6** Specimen obtained from the left posterior temporal lobe

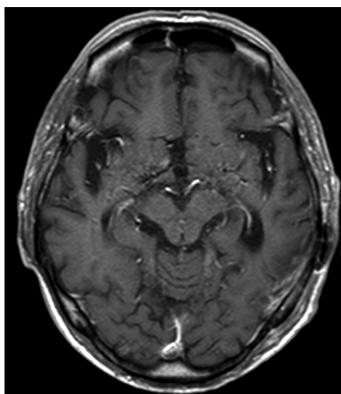
**Fig. 6a:** Hematoxylin and eosin staining showed large Paget cells with bright and abundant cytoplasm in the primary lesions.

**Fig. 6b:** Based on the immunostaining result, the primary lesion was strongly positive for cytokeratin (CK) 7.

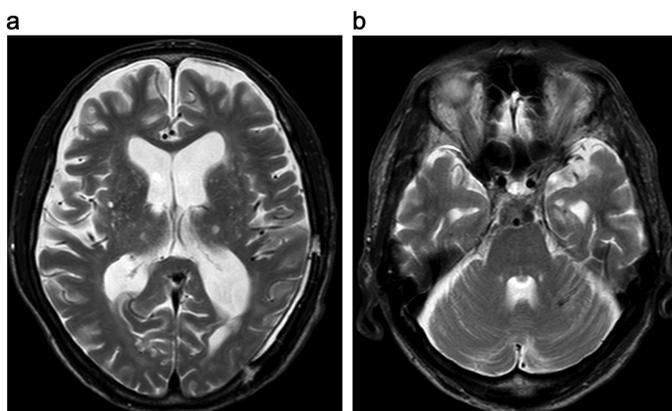
**Fig. 6c:** Negative for CK20.

**Fig. 6d:** Weakly positive for gross cystic disease fluid protein 15.

**Fig. 6e:** The lesion was negative for human epidermal growth factor receptor 2.



**Fig. 7** Postoperative gadolinium-enhanced magnetic resonance imaging: Cerebral lesions have been completely removed.



**Fig. 8** Plain magnetic resonance imaging (MRI) after stereotactic radiosurgery  
**Fig. 8a-8b:** Due to renal dysfunction, a plain MRI was performed. T2-enhanced imaging (a, b) confirmed that there was no recurrence and that the size of the cerebellar lesion decreased.

## DISCUSSION

Extramammary Paget's disease is a skin malignancy, which may arise from the intraepidermal region with apocrine glands. In particular, it develops in the vulva. Only 1439 cases have been recorded in a US database within 35 years (from 1937 to 2007)<sup>1</sup>. The period of stay in the epithelium is considered to be long, and 97.5% of cases do not involve invasion. Furthermore, the prognosis is good if all non-invasive lesions will be removed. The incidence rate of invasion (with distant metastasis) remains low at 2.5%. Metastatic lymph nodes are most commonly observed.<sup>2</sup> Liver, lung, and bone metastases have been reported. However, the reports are limited.<sup>2</sup> The most common type of metastasis is lymphatic metastasis, followed by hematogenous metastasis. In our study, brain metastasis from extramammary Paget's disease is extremely rare. That is, only one case was diagnosed via radiological examination and one case was pathologically diagnosed via tumor biopsy.<sup>3,4</sup> Immunostaining is useful for diagnosis. The diseases diagnosed to differentiate from extramammary Paget's disease are intraepidermal invasion, Bowen's disease, malignant melanoma of the breast, Paget's disease, or other adenocarcinoma. In particular, immunostaining is useful for differentiating Bowen's disease from malignant melanoma. If a specimen is positive for CK7 and GCDFP-15 and negative for CK20, the patient can be diagnosed with extramammary Paget's disease.<sup>5</sup> Chemotherapy using taxanes is provided as post-treatment for patients with invasive disease (distant metastasis).<sup>6,7</sup>

Some patients test positive for human epidermal growth factor receptor (HER)-2, indicating the efficacy of trastuzumab, which is a molecularly targeted drug. However, the prognosis is still poor despite chemotherapy. In this case, the patient was diagnosed with extramammary Paget's disease of the vulva with lymph node metastasis with typical features. The tumor was considered infiltrative, and the prognosis was poor. Invasive disease was considered when new metastases were found after surgery. There are no established treatment for it. If the chemotherapy was effected, cancer might not be metastasized. Moreover, multiple intracranial lesions were observed in this case. The symptoms improved after mass reduction via craniotomy. Furthermore, based on the pathological findings, a definitive diagnosis of extramammary Paget's disease with brain metastasis was made. The possibility of double cancer was also considered. However, the presence of other malignancies was confirmed via PET-CT scan. Since the specimen was negative for

HER-2, trastuzumab was not administered, and radiation therapy was selected as post-treatment. We thought that Novalis could be effective for both brain lesion and lymph node metastasis. Because metastasis lesion caused by another type of cancer could be controlled well. And only few cases reported for extramammary Paget's disease. Although the response to the primary radiotherapy was poor, intracranial lesions could be well controlled.<sup>8</sup>

This information is useful when choosing the treatment strategy for this disease with a limited number of cases. Because only few cases are recorded, treatment guidelines have not been established, and the prognosis of Paget's disease with metastasis is poor.

In this case, patient died due to the primary lesion that was poorly controlled. However, in the case of intracranial metastasis, good control of the primary lesion can prolong the life of individuals with such condition while maintaining quality of life. In this case, the lesion in the left posterior temporal lobe was partially in contact with the cerebellar tent, and it was difficult to distinguish from meningioma based on the imaging results. The tumor was fibrous and hard, indicating the possibility of dural metastasis. Brain metastasis without lung metastasis was observed, and the possibility of dural metastasis was also considered as a mode of metastasis.

Thus, the efficacy of radiation therapy and the mode of metastasis must be assessed in the future.

## FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## DECLARATIONS OF INTERESTS

None.

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