JOURNAL OF NEUROSURGERY:
Case Lessons

J Neurosurg Case Lessons 4(13): CASE22280, 2022
DOI: 10.3171/CASE22280

Skull metastases from extramammary Paget's disease emerging 8 years after initial treatment with no local progression: illustrative case

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BACKGROUND The foci of distant metastasis from extramammary Paget's disease (EMPD) are the lung, liver, truncal bones, vertebrae, and brain. However, skull metastases have not been reported.

OBSERVATIONS The authors treated a patient with calvarial and skull base metastases from EMPD who had undergone wide local resection of EMPD 8 years before, and they report his clinical course.

LESSONS Because EMPD with distant metastasis is fatal, it should be recognized that EMPD can metastasize to the skull even when it seemed to be in remission for several years.

https://thejns.org/doi/abs/10.3171/CASE22280

KEYWORDS extramammary Paget's disease; metastasis; calvarial bone; skull

Extramammary Paget's disease (EMPD) is a rare intraepithelial adenocarcinoma (adenocarcinoma in situ) that arises primarily in areas rich in apocrine sweat glands (e.g., vulva, perianal region, and axilla). It can be managed by wide local resection of the primary lesion with a good prognosis. The 5-year survival rate is about 90% in patients with tumor, node, metastasis (TNM) stages I, II, and IIIa tumors.[1] However, about 20% of patients with EMPD have the regional or distant form, and cases involving distant metastasis have poor prognoses.[1,2] The metastatic organs reportedly include the lung, liver, vertebral bones, and brain.[3–6] Some authors have suggested that the central nervous system is a common metastatic site of EMPD, although skull metastasis has not been reported. We herein describe a patient who developed calvarial metastases 8 years after the removal of EMPD with one sentinel lymph node metastasis.

Illustrative Case

A 77-year-old male with penile and scrotal lesions had been treated by wide local and bilateral sentinel lymph node excision 8 years earlier. He was diagnosed with EMPD with a single lymph node metastasis and was followed up by periodic truncal enhanced computed tomography. The patient felt discomfort and pain in his occipitoparietal region; therefore, he underwent head magnetic resonance imaging (MRI) and was referred to our hospital. The MRI scan showed bilateral occipitoparietal lesions with isointensity on T1-weighted imaging, isointensity on T2-weighted imaging, and mild hyperintensity on diffusion-weighted imaging (Fig. 1A–C). Contrast-enhanced computed tomography indicated that the healthy bone had become filled with cancerous tissue and that the lesions were adjacent to the superior sagittal sinus (Fig. 1D–F). Gallium scintigraphy showed uptake only in the pelvic bone and skull (Fig. 1G). A skull biopsy revealed adenocarcinoma with fused glands or a trabecular pattern, and the tumor cells were immunohistochemically positive for cytokeratin 7 (CK7), GATA3, androgen receptor (AR), gross cystic disease fluid protein 15 (GCDFP15), BerEP4, and carcinoembryonic antigen (CEA) (focal 10%) (Fig. 2A–C). In addition, the penoscrotal epidermis exhibited proliferation of large pagetoid cells with pale cytoplasm (primary EMPD) (Fig. 2D). In the sentinel lymph node tissues, similar tumor cells were present in

ABBREVIATIONS AR = androgen receptor; CEA = carcinoembryonic antigen; CK7 = cytokeratin 7; EMPD = extramammary Paget's disease; GCDFP15 = gross cystic disease fluid protein 15; MRI = magnetic resonance imaging; TNM = tumornodemetastasis.

INCLUDE WHEN CITING Published September 26, 2022; DOI: 10.3171/CASE22280.
SUBMITTED June 30, 2022. **ACCEPTED** August 12, 2022.

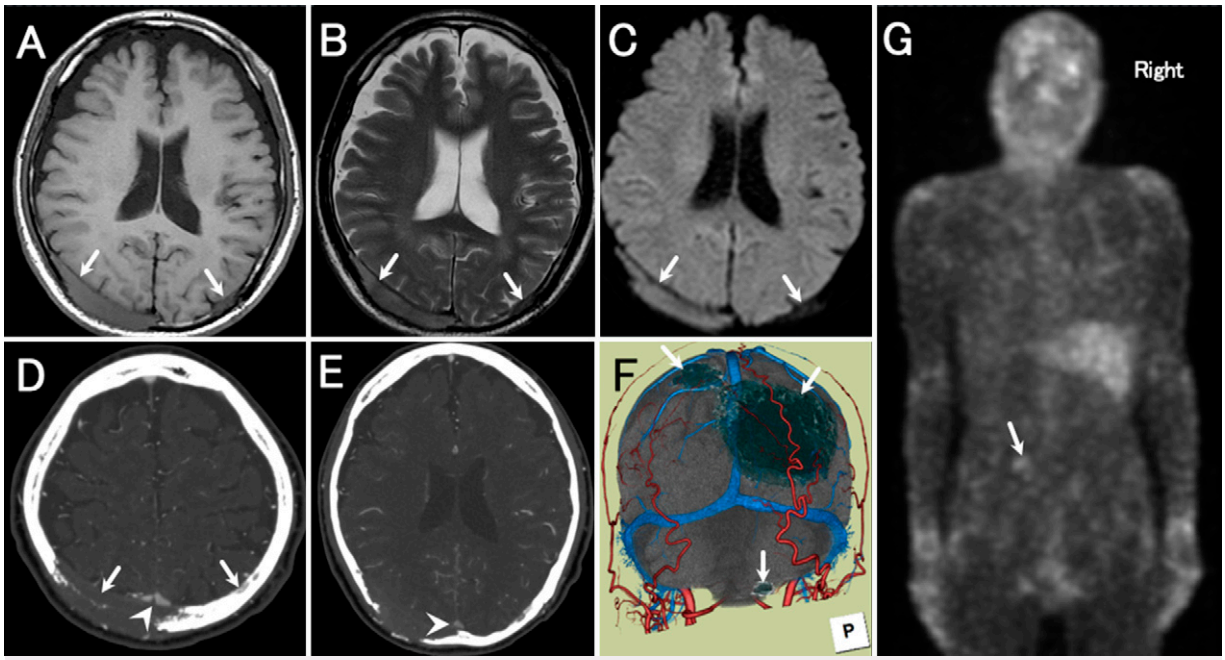

FIG. 1. Presurgical radiological findings. **A–C:** MRI showing bilateral occipitoparietal lesions (*white arrows*) with isointensity on T1-weighted imaging, isointensity on T2-weighted imaging, and mild hyperintensity on diffusion-weighted imaging. **D and E:** Contrast-enhanced computed tomography showing that the bone was replaced by tumors (*white arrows*) and that the lesions were adjacent to the superior sagittal sinus (*white arrowheads*). **F:** A reconstructed image showing three separate lesions (*white arrows*). **G:** Gallium scintigraphy revealed uptake only in the pelvic bone (*white arrow*) and skull.

small solid nests or a fused gland pattern and were immunohistochemically positive for CK7, GATA3, AR, GCDFP15, BerEP4, and CEA (Fig. 2E and F). Therefore, the final diagnosis was distant metastasis from EMPD. We removed the calvarial metastases because of the risk of obstruction of the superior sagittal sinus and pain. We were able to remove the affected bones and replace them with a titanium flap because they were of the intraosseous type and were not adhere to the adjacent skin and dura mater (Fig. 3). The lesions were elastic hard, resembling the consistency of a pencil eraser, and could be damaged by hands. The patient received intensity-modulated radiation therapy (57.5 Gy in 23 fractions) for the tumor bed and skull base lesion as well as chemotherapy (Fig. 4). TS-1

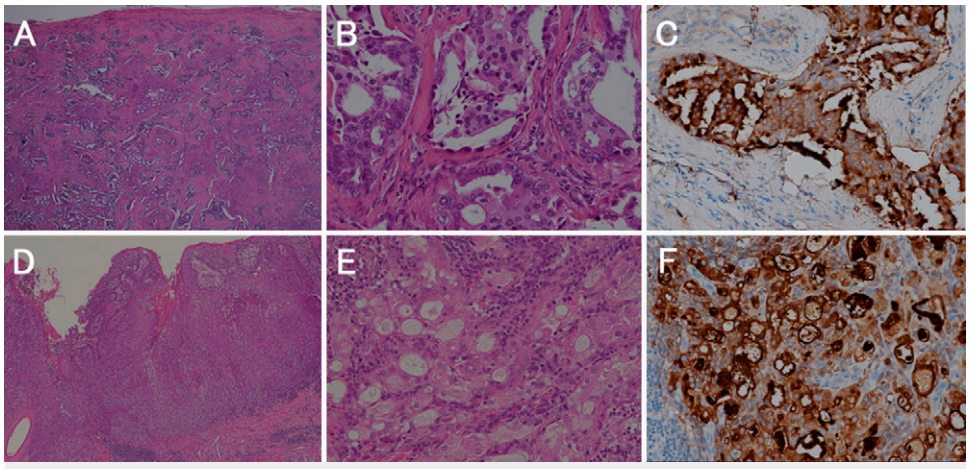

FIG. 2. Histopathological examination and immunohistochemical study. Histopathological examination revealed adenocarcinoma with fused glands or a trabecular pattern in tumor cells obtained from the skull. Hematoxylin and eosin (H&E), original magnification ×20 (**A**) and ×200 (**B**). Immunohistochemical examination showed positivity for gross cystic disease fluid protein of 15 kD (GCDFP15) in cells obtained from the skull (**C**, original magnification ×200). Histopathological examination showed EMPD and adenocarcinoma in the scrotal epidermis (**D**) as well as sentinel lymph node metastasis (**E**). H&E, original magnification ×40 (**D**) and ×200 (**E**). Immunohistochemical examination showed that the metastatic adenocarcinoma in the sentinel lymph node was also positive for GCDFP15 (**F**; original magnification ×200).

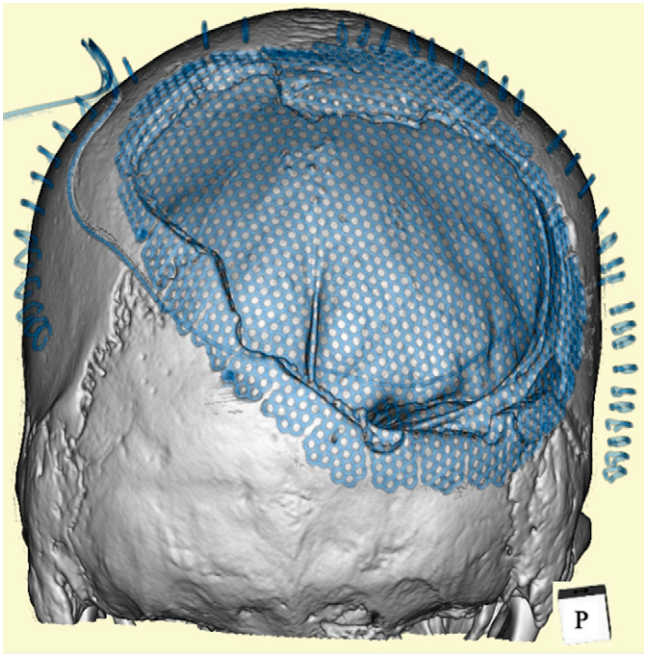

FIG. 3. Postsurgical three-dimensional computed tomography revealed total removal of the occipitoparietal lesions with replacement by a titanium flap.

monotherapy was adopted as a second-line therapy after docetaxel monotherapy failure (progression of visceral metastases). The patient was still alive 12 months after the neurosurgical procedure.

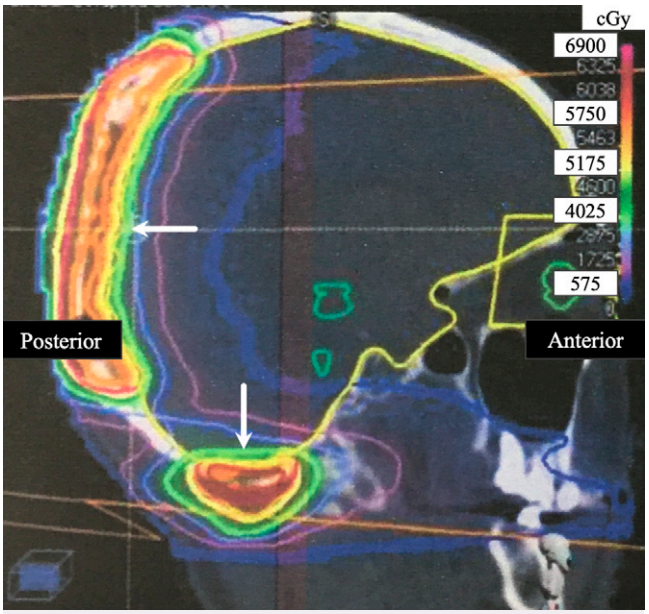

FIG. 4. Sagittal image of the cranial radiation plan. Intensity-modulated radiation therapy (57.5 Gy in 23 fractions) was performed for the tumor bed and skull base lesions (*white arrows*).

Discussion

Observations

To the best of our knowledge, this is the first case of calvarial bone metastasis from EMPD. Although patients with progressive disease (such as those with metastases in multiple organs) may exhibit skull metastasis, our patient had no symptoms other than skull metastasis. Local recurrence and metastases were not detected until 8 years after the patient was thought to be in remission. Invasive EMPD metastasizes mainly by the lymphatic route, and Ohara et al.[1] proposed that early lymphatic spread might be controlled by resection based on the difference in the 5-year survival rate between stages IIIa and IIIb. The presence of skull and pelvic bone metastases without lymph node metastasis suggests another metastatic route; this case prompted us to consider the mechanism of skull metastasis. The vertebral venous system, with its rich, valveless ramifications and connections, widely known as Batson's plexus, is an important metastatic route from the pelvis to the vertebral column, resulting in brain, vertebral, and skull metastases.[7] In this system, the venous pressure is relatively low, and the circulation is slow and subject to reversals of the flow direction. The direction depends on various factors, such as posture, gravity, coughing, straining, and the character of the circulation of the allied systemic, portal, and pulmonary systems.[8] The vertebral venous plexus extends directly to the dural sinuses, which also have valveless structures, and their retrograde blood flow may allow cancer cells to reach the parameningeal tissues.[9] Both brain metastases and calvarial metastases could occur by this route.

Distant metastases of EMPD are often fatal. In a study by Yoshino et al.,[10] the 1-year overall survival rate was 75.0%, and the median overall survival duration was 16.6 months. Some authors reported brain metastases with progressive EMPD in 2020, and vertebral bone metastasis was found to be a prognostic factor for dissemination in the central nervous system.[4–6,11] In comparison, metastatic skull tumors from prostate cancer or breast cancer are widely known to occur, and the median overall survival rates are 23 months and 15 months, respectively.[12,13] Therefore, given the poor prognosis of distant metastases of EMPD and metastatic skull tumors, we should recognize that EMPD can metastasize to the calvarial bone and thus should ensure early diagnosis, treatment, and care.

Lessons

Some cases of EMPD may disseminate to the skull by the vascular route, even when the disease seems to have been in remission for several years.

Acknowledgments

We appreciate the doctors who treated the patient in the Department of Dermatology, Kyoto University Hospital, for a long time. We thank Angela Morben, DVM, ELS, from Edanz for editing a draft of the manuscript.

References

1. Ohara K, Fujisawa Y, Yoshino K, et al. A proposal for a TNM staging system for extramammary Paget disease: retrospective analysis of 301 patients with invasive primary tumors. *J Dermatol Sci.* 2016;83(3):234–239.

2. Herrel LA, Weiss AD, Goodman M, et al. Extramammary Paget's disease in males: survival outcomes in 495 patients. *Ann Surg Oncol.* 2015;22(5):1625–1630.
3. Dai B, Kong YY, Chang K, et al. Primary invasive carcinoma associated with penoscrotal extramammary Paget's disease: a clinicopathological analysis of 56 cases. *BJU Int.* 2015;115(1):153–160.
4. Yamashita C, Yoshino K, Oaku S, et al. Bone metastases could be predictive factors of central nervous system metastases in extramammary Paget's disease. *J Dermatol.* 2020;47(4):e130–e131.
5. Fernandes L, Graça J, de Matos LV, et al. Metastatic extramammary Paget disease, a remarkable clinical case and a brief review of a rare disease. *Dermatol Reports.* 2020;12(2):8841.
6. Fusumae T, Fukuda K, Hirai I, et al. Outcomes in patients with extramammary Paget disease with brain metastasis: a retrospective analysis. *J Am Acad Dermatol.* 2020;83(6):1832–1834.
7. Batson OV. The function of the vertebral veins and their role in the spread of metastases. 1940. *Ann Surg.* 1940;112(1): 138–149.
8. Anderson R. Diodrast studies of the vertebral and cranial venous systems to show their probable role in cerebral metastases. *J Neurosurg.* 1951;8(4):411–422.
9. Kokkoris CP. Leptomeningeal carcinomatosis. How does cancer reach the pia-arachnoid? *Cancer.* 1983;51(1):154–160.
10. Yoshino K, Fujisawa Y, Kiyohara Y, et al. Usefulness of docetaxel as first-line chemotherapy for metastatic extramammary Paget's disease. *J Dermatol.* 2016;43(6):633–637.
11. Miura S, Kijima N, Fujimori N, et al. Surgical treatment of brain metastasis of extramammary Paget's disease: a case report. *NMC Case Rep J.* 2020;7(4):189–193.
12. Laigle-Donadey F, Taillibert S, Martin-Duverneuil N, Hildebrand J, Delattre JY. Skull-base metastases. *J Neurooncol.* 2005;75(1):63–69.
13. Mitsuya K, Nakasu Y, Horiguchi S, et al. Metastatic skull tumors: MRI features and a new conventional classification. *J Neurooncol.* 2011;104(1):239–245.

Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Inada, Nakajima, Miyake, Ishikawa. Acquisition of data: Inada, Nakakuki, Nakajima, Miyake. Analysis and interpretation of data: Nakajima, Miyake. Drafting the article: Inada, Nakajima, Miyake. Critically revising the article: Nakajima, Shibuya, Sakamoto. Reviewed submitted version of manuscript: Nakajima, Miyake, Shibuya. Statistical analysis: Nakajima. Administrative/technical/material support: Nakajima, Miyake. Study supervision: Nakakuki, Nakajima, Miyake. Pathological diagnosis: Shibuya.

Supplemental Information

Previous Presentations

This article was orally presented at the academic meeting of Neurosurgery Kinki 2021 in Japan in September 2021.

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