Case Report

Subcutaneous Sacrococcygeal Anaplastic Ependymoma with Malignant Cystosarcoma Phylloides of the Breast
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Summary
Reports of malignant primary extradural ependymal tumours are exceptionally rare. We report the case of a 30-year-old woman who had an excision of a tumour in the subcutaneous sacrococcygeal region, as well as a right ilioinguinal dissection, 67 months prior to presenting with a mass at the same location. The tumor was excised again, preserving the coccyx. The diagnosis of sacrococcygeal anaplastic ependymoma was made. Eighteen months previously, the patient had been diagnosed as having malignant cystosarcoma phylloides in her right breast mass, which was treated with simple mastectomy. The diagnosis of phylloides was confirmed on re-evaluation of the pathological specimens, as well. An ependymoma with a phylloides tumor has not been previously reported in any patient. In this report, the computed tomography, clinical, and pathological features are discussed.

Key words: Sacrococcygeal, subcutaneous, anaplastic, ependymoma, cystosarcoma phylloides

INTRODUCTION
Primary extradural ependymomas are rare neoplasms, usually of the myxopapillary type, that are World Health Organization (WHO) grade I. Reports of malignant primary extradural ependymal tumors are exceptionally rare.(2)
There are few reported subcutaneous sacrococygeal ependymoma cases of two anaplastic types (WHO grade III)\(^{(9,12)}\) or one ependymoblastic type (WHO grade IV).\(^{(2)}\) Moreover, no cases of ependymoma and phylloides tumor in the same patient have been reported.

In this paper, we report the third case of primary subcutaneous sacrococcygeal anaplastic ependymoma and the first case of ependymoma with cystosarcoma phylloides of the breast.

**CASE PRESENTATION**

A 30-year-old woman was seen due to recent swelling in the sacrococcygeal region, associated with pain and discomfort on sitting. An excision of a tumor at the same location, along with a right ilioinguinal dissection, had been performed 67 months earlier.

Initially, the patient had been misdiagnosed as having malignant melanoma, for which she was treated with 9 courses of cisplatin 20 mg/m\(^2\)/day and dacarbazin 200 mg/m\(^2\)/day for 5 days every 21 days. After a left ilioinguinal dissection 47 months prior to this admission, the patient received 11 courses of temozolomide 200 mg/m\(^2\)/day for 5 days every 28 days as adjuvant chemotherapy for left ilioinguinal metastasis.

Phylloides and surgical treatment

Eighteen months prior to the current admission, the patient was found to have an enlarging mass of the right breast, mostly in the upper-outer quadrant and partly in the upper-inner quadrant, for which she was treated with a simple mastectomy. The spherical, partially macro-calcified mass, which had lobulated and mainly smooth margin and was in a size of 6 cm x 6 cm x 7 cm on imaging, was diagnosed as a malignant cystosarcoma phylloides.

Clinical and radiological findings

At the time of the most recent admission, a solid moveable mass was found in the posterior coccygeal and intergluteal regions. The overlying skin was smooth without any irregularities. Tumor markers, including carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), CA 15-3, CA 125, and CA 19-9 were all negative.

On computed tomography (CT), the subcutaneous mass measured 4.5 cm x 4 cm x 4 cm; it abutted the coccyx and was isodense relative to the muscle tissue (Figure-1).

**Diagnosis of anaplastic ependymoma**

This tumor was excised again, preserving the coccyx. A diagnosis of sacrococcygeal anaplastic ependymoma was made based on pathological and immunohistochemical examinations. It was established that the initial sacrococcygeal mass was actually an anaplastic ependymoma that had recurred.

Pathological findings

Macroscopically, the tumor was encapsulated; the surgical border was tumor-free. Microscopically, the anaplastic ependymoma showed focal micropapillary projections, tumor giant cells, anaplastic ependymal cells with highly brisk mitotic activity (21 mitoses per 10 high power fields), a high cellular density (>800 cells per high power field), large foci of necrosis with pseudopalisading, and perivascular pseudorosettes (Figure-2a).

The tumor cells were diffusely reactive to glial fibrillary acidic protein (GFAP) (Figure-2b), S100 protein, and vimentin; they were negative for cytokeratins and melanoma-associated antigen (HMB45). ABPAS showed alcinothyl with alcian blue stain in the mucin areas located around the malignant cells.

Specimens of the old breast lesion were re-evaluated, and the pathologists (O.U., G.B.) confirmed the diagnosis of malignant phylloides tumor and found no relationship to the sacrococcygeal ependymoma (Figure-3).

**Metastases on follow-up**

Left iliac lymph node dissection was done to remove a 35-mm-diameter metastasis of
the sacrococcygeal primary 5 months later. Although follow-up CT scans showed no local recurrence in the sacrococcygeal region for 15 months after surgery, metastases in the liver and head of the pancreas were noted at 12 months, and there was progression of the metastasis in the head of the pancreas and a new, 2-cm-diameter, peritoneal implant at 15 months.

![Axial CT images](image1.png)

**Figure 1:** Axial CT images. *a:* Image without contrast medium shows the well-defined subcutaneous mass. *b:* Image after the intravenous administration of contrast medium shows the mass with insignificant contrast enhancement

![Pathological features](image2.png)

**Figure 2:** Pathological features. *a:* Cellular areas with micropapillary projections containing fibrovascular cores and mucoid matrices, and poorly differentiated cells with nuclear pleomorphism and atypia (arrow) (HE stain, x400). *b:* The tumor cells reacted strongly to glial fibrillary acidic protein (GFAP), and are stained (GFAP stain, x400)
DISCUSSION
Overall, ependymomas account for 60% of glial spinal cord tumors, though they account for 90% of primary tumors of the filum terminale and cauda equina; in these sites, the majority of ependymomas (30-80%) are of the myxopapillary subtype.\(^3,6\)

While ependymomas are primarily glial tumors of the brain and spinal cord, on rare occasions they may be found outside of the central nervous system (CNS).\(^4\)

Extradural myxopapillary ependymomas are rare; they probably arise from extradural remnants of the filum terminale or the coccygeal medullary vestige.\(^7,13,15\)

Primary extraspinal ependymal tumors that have histological signs of anaplasia are even rarer; they have been found in the sacral region, ovaries, lungs, and in the soft tissues of the anterior lower neck region.\(^2,16\)

An ependymoblastic type, WHO grade IV, subcutaneous sacrococcygeal malignant ependymoma was reported in a 3-year-old boy with Schinzel–Giedion midface-retraction syndrome with lumbar spina bifida occulta and CNS abnormalities who had no metastasis\(^2\); three other reported cases including one presacral ependymoma\(^13\) had anaplastic type, WHO grade III tumors with metastases.\(^12,13\) The present case had an anaplastic type of sacrococcygeal malignant ependymoma with metastases.

Ependymomas can occur under four general situations: metastatic extension from a primary CNS neoplasm; direct extension of a primary ependymoma of the spinal cord, filum terminale, or cauda equina into the soft tissue of the sacrococcygeal area; a primary tumor of the skin or subcutaneous tissue without any demonstrable connection with the spinal cord; and a primary presacral, pelvic, or abdominal tumor.\(^3,6,7\) The third condition was found in the present case.

The origin of extraspinal ependymomas is still unclear. Three hypotheses predominate in the literature: the first proposes that these tumors arise in the sacral region from undifferentiated embryonic cells (ependymal cell rests), the second proposes development caused by heterotopic cells from filum terminale, and the last which is germ cell hypothesis explains how extraspinal ependymomas
could be thought of as monodermal teratomas with exclusive neuroectodermal differentiation.\(^{(8)}\) Of these hypotheses the germ cell origin that has been proposed may explain the rare occurrence of ependymomas in the ovaries and the mediastinum.\(^{(8,11)}\)

To the best of our knowledge, this is the first reported case of an ependymoma in a patient with cystosarcoma phylloides, which is a myoepithelial tumor of the breast. Fibroadenoma and benign phylloides tumor of the breast should be thought in the differential diagnosis of benign side. A leaf-like pattern and hypercellular stroma favor a diagnosis of phylloides tumor, but size alone cannot be used as a distinguishing feature. Primary breast sarcoma and the metaplastic carcinoma of the breast must be distinguished from malignant phylloides tumors. This differentiation can be made since the mixture of elements with the distinctive leaf-like epithelial clefs of phylloides tumor is not seen in other lesions.

Cystosarcoma phylloides has previously been reported in a patient with generalized neurofibromatosis.\(^{(19)}\) Also it has been stated a considerable fraction of spinal ependymomas are associated with molecular events involving chromosome 22 and that mutations in the neurofibromatosis 2 (NF2) gene may be of primary importance for their genesis.\(^{(5)}\) The analysis NF2 tumor suppressor gene, located on 22q12.2 has revealed a high rate of mutations in ependymomas of spinal, nevertheless, the flanking chromosomal region 22q11 may harbor putative ependymoma tumor suppressor gene(s) involved in the evolution and/or progression of ependymomas.\(^{(10)}\) In fact, the studies have indicated an involvement of tumor suppressor genes localized within chromosomal region 22q in spinal ependymomas.\(^{(16)}\) Lacking in genetic analysis, we believe this case may have significance on the genetic pathway of ependymomas.

On histology, myxopapillary ependymomas are characterized by cellular areas mixed with papillary regions containing vascular cores and extensive mucoid matrixes.\(^{(15)}\) Anaplastic ependymomas exhibit high mitotic activity, often accompanied by microvascular proliferation and pseudo-palisading necrosis.\(^{(17)}\) Perivascular rosettes are a histological hallmark, though ependymal rosettes are rare, and frequently absent.\(^{(17)}\) In the present case, the tumor was found to have typical perivascular rosettes, whereas ependymal rosettes were not present. The histological distinction between ependymoma WHO grade II and anaplastic ependymoma WHO grade III is not clear-cut.\(^{(2)}\) Nevertheless, in the present case, the tumor showed obvious signs of anaplasia (high cellularity, brisk mitotic activity, and necrosis), which allowed a definitive diagnosis to be made.

In literature, nuclear pleomorphism was not present in the lung metastasis of the subcutaneous sacrococcygeal anaplastic ependymoma although the primary tumor showed this; which supported the theory of Sonneland et al. about lack of dedifferentiation of ependymoma.\(^{(12)}\) Conversely, the inguinal lymph node metastasis had nuclear pleomorphism in the other subcutaneous sacrococcygeal anaplastic ependymoma but the primary tumor had generally nuclear unimorphism.\(^{(9)}\) Differently, nuclear pleomorphism was present in both of the primary and ilioinguinal lymph node metastasis of the current case, which did not support Sonneland et al.’s theory either.

As in the present case, ependymomas typically react positively to GFAP, S100, and vimentin.\(^{(8,15)}\) Also the diagnosis of myoepithelioma or myoepithelial carcinoma that is GFAP-positive can be excluded with negative cytokeratin stain.\(^{(16)}\) The immunoprofiles of anaplastic ependymoma resemble those of conventional ependymoma, but GFAP expression may be reduced in anaplastic ependymoma.\(^{(17)}\) In the present case, there
was no reduction of GFAP expression by the anaplastic cells.

The differential diagnosis of subcutaneous sacroccygeal ependymoma includes pilonidal cyst, teratoma, chordoma, lipoma, sweat gland tumor, sarcoma, metastatic mass, serous papillary carcinoma, giant cell tumor, neurofibroma, abscess, and meningocele. A subcutaneous sacroccygeal ependymoma is commonly misdiagnosed as a pilonidal cyst or sinus, but imaging studies should discriminate between cystic and solid lesions. In the present case, the first lesion was initially misdiagnosed as a malignant melanoma on pathological examination in another institution; therefore, malignant melanoma should be included in the differential diagnosis of subcutaneous sacroccygeal ependymoma.

The imaging features of ependymomas located outside of the CNS have not been extensively reported. On contrast enhanced CT, a mass of soft tissue density, which enhances after intravenous contrast administration, is seen. Focal necrosis, cystic degeneration, and/or hemorrhage may result in an inhomogeneous lesion with mixed signal intensity on magnetic resonance imaging (MRI). In the present case, on CT, the isodense mass showed only minor contrast enhancement due to the presence of myxoid and necrotic areas. Anaplastic ependymomas tend to remain well demarcated, but are occasionally frankly invasive. In the present case, the lesion was well demarcated on CT and on pathological examination.

In cases with ependymomas of either myxopapillary or anaplastic subtype, recurrences and distant metastases are common and can occur many years after the initial diagnosis. This suggests a relationship with the site of primary origin rather than with the histology. Accordingly, intradural lumbosacral ependymomas can spread throughout the CNS but rarely metastasize beyond it; extradural ependymomas seldom disseminate within the CNS, but they pose a significant risk for systemic metastases. The risk of metastases also depends on the tumor's specific extradural location; dorsal subcutaneous tumors have a greater risk for metastases than presacral tumors.

It has been reported that high cell density and brisk mitotic activity are independent variables for survival. However, currently, there are no reliable clinical or histological features that can help predict the development of metastases. We consider that the recurrence and metastases in the case were most likely due to both the tumor's specific extradural location and its anaplastic nature.

The most common metastatic sites of ectopic subcutaneous sacroccygeal ependymomas are the lungs and the inguinal lymph nodes. The present case had ilioinguinal lymph node metastases, but no lung metastases. Metastases in the case were to the liver, peritoneum and head of pancreas as well. To our knowledge metastasis to pancreas has not so far been reported in any ependymoma.

Metastatic disease from extradural ependymomas appears to carry a poor prognosis due to a lack of response to adjuvant therapies. Thus, when feasible, gross-total resection is the treatment of choice; radiotherapy is more controversial as it does not appear to be as effective in extradural ependymomas as it is in intradural ependymomas. In the absence of metastatic disease, complete excision of the tumor with regional lymph node dissection will usually result in prolonged disease-free survival.

There is no evidence that these tumors respond to chemotherapy. However, it has been recently suggested that the use of selective cyclooxygenase-2 (COX-2) inhibitors may provide a new therapeutic strategy for spinal cord ependymomas due to their inhibition of the COX-2-mediated angiogenesis.
Surgical removal of the coccyx may be required if the tumor is attached to it. (1,8,11)

CONCLUSION
Anaplastic ependymoma, despite its rarity, should be considered in the differential diagnosis of the subcutaneous sacrococcygeal malignant tumors, since it is resistant to radiotherapy and currently available chemotherapy. Coexistence of an extradural anaplastic ependymoma with a cystosarcoma phylloides of breast is important as their genetic predisposition may be significant in the understanding of molecular oncogenesis. More reports and research are needed for this respect.

REFERENCES

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