Case Report

Calcifying pseudoneoplasm of the neuraxis (CAPNON) associated with neurenteric cyst. An autopsy case showing unusual fatal outcome

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A 53-year-old man with a history of an untreated brain mass was taken to Toyama Prefectural Central Hospital by emergency transport. Computed tomography revealed an intracranial hypo-attenuated lesion exhibiting mass effect. Several calcified foci were observed around the lesion. His radiographical diagnosis was meningioma with calcification and edema. He suddenly showed tonic seizure after admission; therefore an emergency craniotomy was performed. However, he unfortunately died due to advanced cerebral edema. Microscopic findings of the surgically obtained materials were consistent with neurenteric cyst (NC). Intracranial hard masses were found adjacent to NCs, and the masses were composed of fibrous cartilage-like matrix with extensive linear calcification and the presence of surrounding round-to-oval epithelioid cells. Thus, calcifying pseudoneoplasm of the neuraxis (CAPNON) associated with NC was considered the most appropriate diagnosis of the present case. To the best of our knowledge, this is the first report of such a case. The present case suggests that delay of treatment might cause a poor outcome, at least in CAPNON associated with NC. Careful investigations, including the underlying pathology, may be essential when considering the etiology of CAPNON and its treatment strategies.

Key words: autopsy, calcifying pseudoneoplasm of the neuraxis, immunohistochemistry, neurenteric cyst, pathology.

INTRODUCTION

Calcifying pseudoneoplasm of the neuraxis (CAPNON) is a rare calcified tumefactive lesion that can occur in the brain or spinal cord.1–3 The growth of CAPNON is generally indolent, and the majority of reported cases show a benign clinical course after complete or subtotal surgical excision.2,3 Therefore, the etiology and natural course of CAPNON have not yet been fully understood. A recent study reported that many CAPNON cases have dual pathology, which may be associated with its etiology.1 Here, we report a rare autopsy case of CAPNON that was completely free of any medical interventions in the critical period and was associated with a neurenteric cyst (NC), which is an endoderm-derived congenital lesion.4

CLINICAL SUMMARY

A 53-year-old man complaining of head pain and systemic paralysis and seizure in both legs was taken to Toyama Prefectural Central Hospital by emergency transport. Approximately 13 years previously, he had visited Toyama University Hospital because of hyposmia and headache. Computed tomography (CT) and magnetic resonance imaging (MRI) revealed a calcified mass in the left anterior cranial base (Fig. 1A–E). The radiographical diagnosis was meningioma with calcification. Although surgical treatment was proposed, he refused surgery and did not visit the hospital again. According to information from his family, his personality gradually changed, and he had started to complain of several additional symptoms in the last few years, including dizziness, tinnitus, and neck pain. He had also shown abnormal behavior in the last few months, such as suddenly screaming or talking to strangers. At the time of emergency transport, his consciousness was clear, and conversation was possible. CT revealed an intracranial hypo-attenuated lesion without contrast enhancement, exhibiting mass effect (Fig. 1F–J).
Additionally, several calcified foci were observed around the lesion. The radiographical diagnosis was meningioma with calcification and edema. At midnight of the day he was hospitalized, he suddenly showed tonic seizure and anisocoria (2 mm and 4 mm in diameter on the right and left pupils, respectively); the neurosurgeon therefore decided to perform an emergency craniotomy. However, cerebral edema progressed continuously despite intensive care, and he died 12 days after surgery. After obtaining informed consent of the family, postmortem pathological examination was performed.

**PATHOLOGICAL FINDINGS**

During surgery, a well-demarcated cystic lesion, containing pus-like fluid and semisolid brittle whitish materials, F was observed (Fig. 2A). Partial resection of the lesion and internal and external decompression were performed. Histological examination of the surgical specimen on hematoxylin and eosin (HE) staining revealed a single layer of ciliated columnar epithelium without cellular atypia (Fig. 2B).

Immuno-histochemical examination was performed using primary antibodies against cytokeratin 7 (CK7) (mouse monoclonal, clone OV-TL-12/30; Dako, Glostrup, Denmark; 1:50), CK20 (mouse monoclonal, clone ks20.8; Dako; 1:250), vimentin (mouse monoclonal, clone V9; Dako; 1:100), S-100 protein (rabbit polyclonal, Cat. No. Z0311; Dako; 1:1000), epithelial membrane antigen (EMA) (mouse monoclonal, clone E29; Dako; 1:100), cluster of differentiation 68 (CD68) (mouse monoclonal, clone PG-M1; Dako; 1:100), pancytokeratin (mouse monoclonal, clone AE1/AE3; Dako; 1:100), low-molecular weight CK (mouse monoclonal, clone CAM5.2; BD Biosciences, Franklin Lakes, NS, USA; 1:1000), glial fibrillary acidic protein (GFAP) (mouse monoclonal, clone 6F2; Dako; 1:200), somatostatin receptor type 2 (SSTR2) (rabbit polyclonal, Cat. No. EP149; Nichirei, Tokyo, Japan; 1:200), and amyloid-beta precursor protein (APP) (mouse monoclonal, clone OTI2B10; ORIGENE, Rockville, MD, USA; 1:200).

Immunohistochemically, the ciliated columnar epithelial cells underlying the inner surface of the cystic lesion were positive for CK7 and CK20, but negative for GFAP and S-100 protein (Fig. 2C–F; Table 1). Cytological
examination of the intracystic fluid identified no malignant cells. These findings are consistent with NC.

At autopsy, a large bone defect was observed in the midline of the anterior cranial fossa (Fig. 3A). The brain weighed 1542 g and exhibited severe encephalomalacia. Moreover, there were several hard masses, mainly in the left frontal lobe.

Microscopically, the hard masses were composed of fibrous cartilage-like matrix and extensive linear calcification and partial ossification (Fig. 3B). NCs were also observed adjacent to hard mass lesions that were sampled at autopsy (Fig. 3C). Various pathological appearances, containing collagen fibers and hyaline cartilage-like stroma, were identified beneath the hard masses (Fig. 3D). Here, there were foci of granulation tissue, containing abundant lymphocytes and macrophages, and necrotic tissue with marked neutrophil infiltration (Fig. 3E). The hard masses were surrounded by round-to-oval epithelioid cells and giant cells (Fig. 3F). Immunohistochemically, these cells (Fig. 4A) were diffusely and strongly positive for vimentin (Fig. 4B), focally positive for EMA (Fig. 4C), CD68 (Fig. 4D), and S-100 protein (Fig. 4E), but negative for SSTR2 (Fig. 4F), pancytokeratin (Fig. 4G), low-molecular weight cytokeratin, and GFAP (Fig. 4H). On the other hand, the meningotheelial hyperplastic lesion adjacent to the CAPNON was diffusely and strongly positive for vimentin (Fig. 4B), EMA (Fig. 4C), and SSTR2 (Fig. 4F), but negative for CD68, S-100 protein, pancytokeratin (Fig. 4G), low-molecular weight cytokeratin, and GFAP (Fig. 4H). Immunohistochemical findings are summarized in Table 1. Many APP-positive cells, indicating the presence of cell damage, were observed in the brain tissue (Fig. 4I) in addition to necrosis of the pituitary gland (Fig. 5).

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Table 1  Results of immunohistochemical examination in the surgical and autopsy specimens

|                        | Positive                                      | Negative                           |
|------------------------|-----------------------------------------------|------------------------------------|
| Surgical materials (Neurenteric cyst) | CK7 (diffuse, strong)                         | GFAP                               |
|                        | CK20 (diffuse, weak)                          | S-100 protein                      |
| Autopsy materials (CAPNON) | Vimentin (diffuse, strong)                    | CK AE1/AE3                         |
|                        | EMA (focal, weak)                             | LMW-CK                             |
|                        | CD68 (focal, strong)                          | GFAP                               |
|                        | S-100 protein (focal, moderate)               | SSTR2                              |
| Autopsy materials (Meningothelial hyperplasia) | Vimentin (diffuse, strong)                    | pan-CK                             |
|                        | EMA (diffuse, strong)                         | LMW-CK                             |
|                        | SSTR2 (diffuse, strong)                       | GFAP                               |
|                        | CD68                                           | S-100 protein                       |

CAPNON, calcifying pseudoneoplasm of the neuraxis; CK, cytokeratin; EMA, epithelial membrane antigen; GFAP, glial fibrillary acidic protein; LMW-CK, low-molecular weight cytokeratin identified by CAM5.2; NC, neurenteric cyst; pan-CK, pancytokeratin identified by AE1/AE3; SSTR2, somatostatin receptor type 2.

Fig 3  Gross (A) and histological (B-F) findings on postmortem pathological examination. (A) A large bone defect is observed in the midline of the anterior cranial base (arrowhead). (B) A hard mass is composed of fibrous cartilage-like matrix and extensive linear calcification and partial minimal ossification. (C) The inner surface of a cystic lesion is lined by a single-layer of ciliated columnar epithelial cell adjacent to the calcified mass lesion. (D) A hard mass contains collagen fibers and hyaline cartilage-like stroma with dural attachment (arrowheads). (E) Adjacent to the calcified lesion (right side), both granulation tissue containing many capillaries (center) and necrotic tissue containing inflammatory cells, including neutrophils and macrophages (left side), are observed (inset at a higher magnification). (F) Round-to-oval epithelioid cells and giant cells surround the calcified lesion. Scale bars: 2 mm (B, D); 200 μm (E, F); 100 μm (C).
DISCUSSION

Supratentorial NC is rarely associated with calcification, and we were unable to find any previous report of obvious mass lesions associated with NC. We consider that CAPNON associated with NC is the most appropriate pathological diagnosis of the present case. To the best of our knowledge, this is the first report of CAPNON associated with NC. The enlarged and newly appearing calcified lesions on CT performed before surgery could indicate that CAPNON development has been associated with congenital NC in the current case. Prolonged and/or recurrent inflammation of NC and/or its secretion product in the present case might thus contribute to the occurrence and development of CAPNON. It is notable that synovial cysts are frequently associated with spinal CAPNON. Therefore, investigations targeting cystic lesions may be important for elucidating the etiology of CAPNON.

In the present case, slowly progressive cerebral edema and local inflammation with the development of CAPNON may have reached an irreversible level because of the long-term untreated period. Necrosis of the pituitary gland is also associated with advanced brain edema, and may cause pituitary apoplexy in the terminal phase.

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The present case may demonstrate the importance of early surgical resection for CAPNON, even though the clinical course of CAPNON is essentially benign. Careful investigation of the relationship between NC and CAPNON is needed, and may be useful for elucidating the etiology of CAPNON in the future.

The radiographical diagnosis at the hospital at both visits was meningioma with calcification. The present case thus suggests that CAPNON is an important differential diagnosis for meningioma with calcification from both clinical and pathological aspects, even if multiple calcified lesions, which are considered rare in CAPNON, are found. Although we identified epithelioid cells that were positive for EMA and vimentin, as shown in a previous report, the lesion should not be diagnosed as meningioma because these cells were also positive for various markers, including S-100, GFAP, nestin, and histiocytic markers such as CD68 and CD163. The immunohistochemical features of the present case, especially the expression of SSTR2, which is the most sensitive and specific marker for meningiomas, were different from those previously shown in meningiomas. SSTR2 may thus be useful for distinguishing CAPNON from calcified meningioma. Interestingly, although the meningothelial cells are one of the possible candidates for the origin of CAPNON, the immunohistochemical results between CAPNON and meningothelial hyperplasia in this study were quite different. Thus, CAPNON may be a condition different from mere meningothelial hyperplasia, and further investigation is needed to identify its origin and pathogenesis.

In conclusion, we reported a case of fatal CAPNON that was likely associated with NC; marked cerebral edema related to prolonged local inflammation was evident in the brain. The present case suggests that no treatment cause a poor outcome, at least in some CAPNON cases and especially when CAPNON is associated with NC. Careful investigation, concerning the underlying pathology, may be essential for understanding the etiology of CAPNON, which might contribute to the investigation of therapeutic strategies for CAPNON in the future.

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ETHICS STATEMENT

Written consent was obtained from next kin and guardian. All procedures performed in studies in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.
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