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ORIGINAL ARTICLE

Proximal-Type Epithelioid Sarcoma in Skull Base: a Pathological Diagnosis Challenge with Other Intracranial Tumors

Duan Zejun[1] · **Yao Kun**[2] · **Lu Dehong**[2] · **Qi Xueling**[1]

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Abstract Proximal-type ES (PES) is a rare and aggressive sarcoma originated from soft tissues with uncertain differentiation. It mainly affects middle-aged patients and often locates in proximal extremity and deep-seated tissues. Only one case of PES located in the skull base has been reported to date. Herein, we report two cases of PES occurred in the middle cranial fossa in two middle-aged Chinese women. Microscopically, the tumors were consisted of epithelial-like cells with or without rhabdoid cells. And frequent mitotic activity and coagulation necrosis were present. Immunohistochemically, tumor cells in the two cases were positive for vimentin, AE1/AE3, epithelial membrane antigen (EMA), CD34, and synaptophysin. A few number of tumor cells expressed CD56. They were completely negative for integrase interactor-1 (INI1). Besides, TP53 positive cells were observed (>50%) in the two cases. The MIB-1 proliferation index was high up to 50–70%. Fluorescence in situ hybridization showed the monoallelic deletions of INI1. Intracranial PES is needed to identify with other mimic tumors, especially rhabdoid meningioma, epithelioid MPNST and adult AT/RT. The prognosis of the two patients was very poor. They died respectively less than a month and half a month after surgery. Tumor grew rapidly and was easy to infiltrate into the surrounding tissues. It may suggest that the prognosis of PES occurred at the base of skull was worse than in other sites.

Keywords Proximal type epithelioid sarcoma · Middle cranial fossa · Skull base · Atypical teratoid/rhabdoid tumour

Duan Zejun and Yao Kun contributed equally to this work

✉ Qi Xueling
xszqxl169@163.com

Duan Zejun
Night0329@126.com

Yao Kun
yaokun2007@163.com

Lu Dehong
ludehong20162017@163.com

[1] Department of Pathology, San Bo Brain Hospital, Capital Medical University, Beijng, People's Republic of China

[2] Department of Pathology and Molecular Biology Laboratory, San Bo Brain Hospital, Capital Medical University, Haidian District, Beijng, People's Republic of China

Background

Epithelioid sarcoma (ES) is a kind of rare and aggressive soft tissue sarcoma with uncertain tissue source. ES was firstly described by Enzinger in 1970 [1]. It is a rare soft-tissue sarcoma typically presents as a subcutaneous or deep dermal mass in distal portions of the extremities in adolescents and young adults. Other cases were reported thereafter, and the relevant studies referred these tumors as synovial sarcoma, tendon sheath giant cell sarcoma, etc. [2, 3]. In 1997, Guillou named this kind of tumor as proximal type epithelioid sarcoma (PES) according to the location of tumors. They have some different histological features and biological behaviors from conventional ES [4]. The World Health Organization (WHO) classification 2013 of soft tissue tumor divided ES into distal and proximal types. The immunophenotype, tissue structure and ultrastructure were not significantly different between them. But they differ from occurrence site, cell morphological characteristics and prognosis [5]. PES mainly affect middle-aged patients and often occurred in proximal extremity and deep-seated tissues, such as pelvis, perineum, and genital tract. It is characterized by proliferation of epithelioid-like tumor cells with or without rhabdoid cells, but has no granuloma-like pattern in distal ES

[4, 6–13]. We found that only one case of PES occurred in the skull base has been reported to date [14]. Herein, we report two cases of PES occurred in the middle cranial, and the pathological features and differential diagnosis of other mimic tumors in the intracranial are discussed.

Case Presentation

Clinical History

Case 1

A 47-year-old woman had a medical history of headache with nausea, vomiting, polyuria and polydipsia for two months. She also had right eyelid ptosis, shadows and left eye fission narrowed for more than 20 days. Her daily water intake was 4000-5000 ml. Daily urine output was about 4000 ml. She lost 20 kg during illness. Physical examination found bilateral eyelid ptosis and that right eye could not open. The right pupil diameter was 5.0 mm with loss of light reflex. The right eye abduction and adduction were limited and horizontal visual was ghosted. Laboratory tests showed that the thyroid hormone levels were reduced (free T4 0.65 ng / dl, TSH 0.003uIU / ml). The computed tomography (CT) and magnetic resonance imaging (MRI) scan of his head showed a abnormal lobulated and lumpy signal in intrasellar, suprasella and sphenoid sinus. Bilateral cavernous sinus were involved and saddle back bone was destructed. The size of lesion was about 40 × 30 × 46 mm. The lesion presented isodensity with slightly lower density signal in CT scan (Fig. 1a). In MRI, the lesion presented slight hyperintense T1-weighted signal and uneven T2-weighted signal, with slightly patchy hypointense T1-weighted and T2-weighted signal (Fig. 1b, c). After enhancement, the lesion was heterogeneously significantly enhanced (Fig. 1d).

During neurosurgical resection, we found that the tumor was located in the intrasellar and suprasella. Partial tumor broke into the anterior part of the third ventricle. The tumor was grayish red, with soft texture and medium blood supply. There was no obvious boundary between tumor and pituitary. The tumor underwent nearly total excision and the size was about 4.5× 4 × 3.5 cm.

After surgery, the patient had bilateral ptosis, and bilateral pupil diameter were both 4.0 mm. Besides, light reflex of the right eye was lost and left side of the light reflex was slow. The abduction and adduction of the right eye were limited too. Laboratory tests showed high sodium, urine output, low hormone levels (such as, cortisol, TSH, total T3 and free T3). The condition of the patient was not stable, but the patient and family required for discharge due to poor economic conditions.

Case2

A 52-year-old woman had a medical history of headache associated with fever for one week after seller tumor surgery two months later. Two months ago, she suffered from a painful headache in the occipital region and neck. Headache could be alleviated for 2–3 h by painkiller (species unknown). In local hospital, head CT and MRI scan revealed an occupying lesion in the saddle area (Fig. 2a–d). After then, she performed saddle area tumor resection through a single nostril transsphenoidal. After surgery, headache was relieved, but she gradually had drooping right eyelid. One month later, the tumor recurred and she underwent partial sellar tumor resection again. The pathological diagnosis after two surgeries was considered to be an atypical pituitary adenoma after excluding metastatic carcinoma. Then, the patient took positron emission tomography-computed tomography (PET-CT) examination which showed no metabolic lesions. One week ago, the headache was aggravated, accompanied by fever. Physical examination showed right eye blindness and right eyelid ptosis. Once more, head CT showed a mass with slightly uneven high signal in the sphenoid sinus, intrasella and suprasella, with CT value 43Hu and size

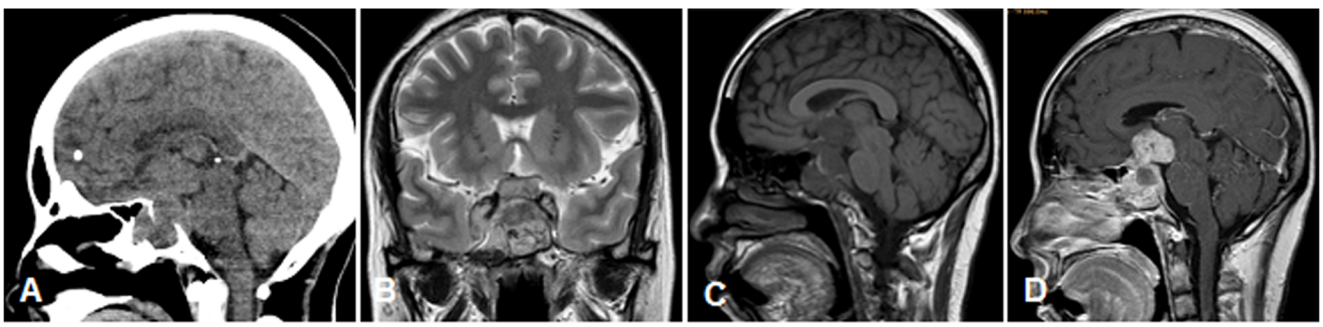

Fig. 1 Head CT and MRI of case 1. CT (**a**) showed isodensity signal within the sella, saddle and sphenoid sinus, and focal slight hypointensity; bone destruction of saddle back was found. MRI (**b**, **c**) revealed a lobulated and lumpy abnormal signal in the sella and saddle, with uneven T2-weighted signal intensity and slight hyperintense T1-weighted signal intensity, patchy slightly hypointense T1-weighted and T2-weighted signal in the lesion. Bilateral cavernous sinus involved. The lesion broke into cistern and the three ventricle anterior. After enhancement, the lesion showed heterogeneous significantly enhanced (**d**)

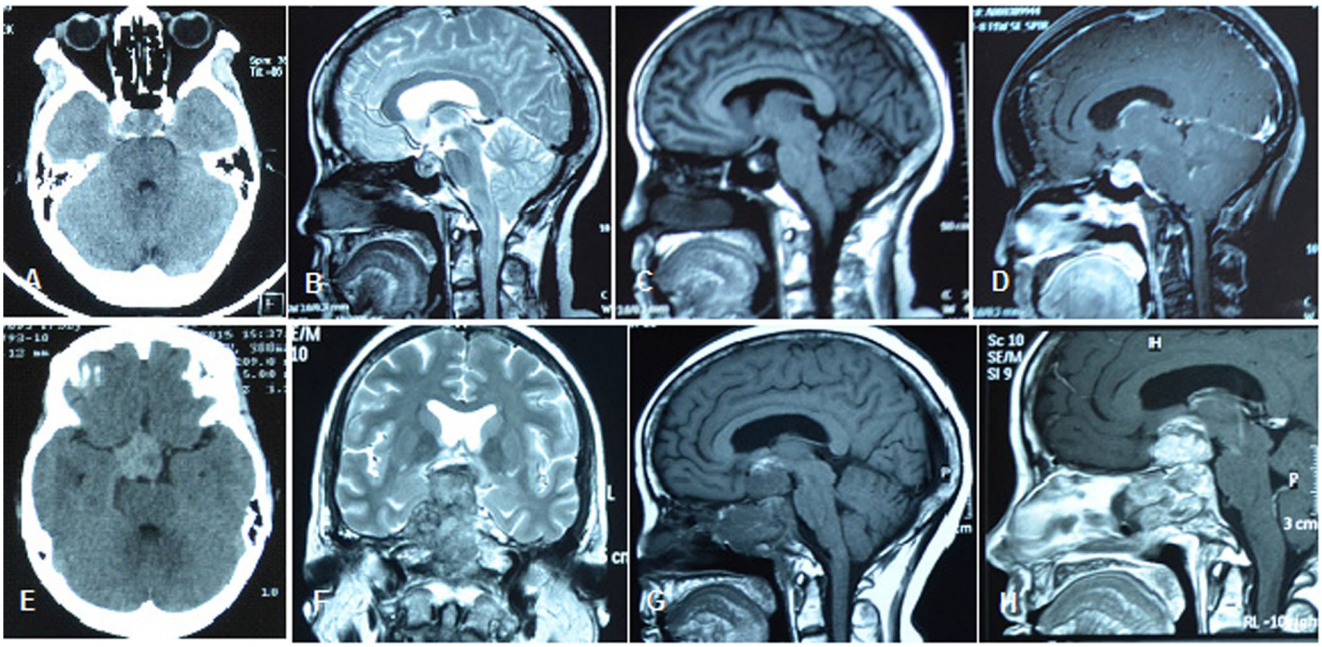

Fig. 2 Head CT and MRI of case 2. The first pre-operative CT and MRI (A-D); CT showed uneven density signal in the sellar (**a**). MRI showed uneven slight hypointense T2-weighted signal intensity (**b**) and hyperintense T1-weighted signal intensity (**c**). After the enhancement, the lesion was significantly enhanced (**d**). The third pre-operative CT and MRI (**e-h**); Head CT showed a lumpy slightly high density signal in the sphenoid sinus, sella and saddle (**e**). MRI showed a large shape of slight hypointense T2-weighted signal intensity (**f**) and uneven hyperintense T1-weighted signal intensity, with small pieces of hypointense T1weighted signal intensity (**g**). Lesions involved the right cavernous sinus, and broke into the three ventricle. After the enhancement, the lesion was large patchy uneven enhancement (**h**)

for 48 × 22 × 47 mm, violations of bilateral cavernous sinus (Fig. 2e). In MRI, the mass had uneven hyperintense T1-weighted signal and slight hypointense T2-weighted signal, with small pieces of hypointense T1-weighted signal intensity (Fig. 2f, g). It involved the right cavernous sinus, and broke into the third ventricle. After the enhancement, it showed large, patchy and ueven enhancement (Fig. 2h).

During the surgery, we found that the tumor was located in the intrasellar and suprasella, which was gray red, medium texture, with obscure boundary and rich blood supply. More than 90% of the tumor was resected, and the size was about 3 × 4 × 4 cm.

After surgery, she recovered well. The vital signs were stable, but mental state was poor. Left eye vision was dropped by rough examination. Limb muscle strength was grade IV with balanced ataxia.

Histologic and Immunohistochemical Examinations

Two patients had applied for intraoperative rapid frozen pathological exams during surgery. The frozen sections showed intensive proliferation of tumor cells (Figs. 3a and 4a). The tumor cells were large, with abundant cytoplasm, large and atypia nucleus, some were with obvious nucleoli. Some tumor cells were similar to rhabdoid cells. Numerous mitotic figures and necrosis areas were present. We consider them to be malignant tumor. But it was difficult to figure out which type it is.

On histology, two cases had similar morphological changes (Figs. 3a, b and 4a, b). Microscopically, tumors were characterized by proliferation of epithelial-like cells with some rhabdoid cells. Rhabdoid tumor cells were more obvious in case 2. The epithelial-like tumor cells were characterized by large, abundant amphophilic cytoplasm, vesicular nuclei with prominent central single nucleoli. The rhabdoid cells with eccentrically placed nuclei, abundant eosinophilic cytoplasm, and intracytoplasmic, paranuclear hyaline inclusions were observed. High mitotic activity and foci or sheet coagulation necrosis were present. In some part of the region, there were dilated thin-walled vessels similar to haemangiopericytoma (Fig. 3b).

On immunohistochemistry (IHC), the tumor cells were diffusely positive for Vimentin. Partial cells were positive for cytokeratin (AE1/AE3), epithelial membrane antigen (EMA), and synaptophysin (Syn). Almost all cells were positive for AE1/AE3 in case 1, while only 10% were positive in case 2 (Fig. 3d and 4d). About 30–50% tumor cells were positive for EMA in both cases (Fig. 3e and 4e). Syn was weakly positive in case 1, while strong positive in case 2 (Fig. 3f and 4f). Focal tumor cells were membranously positive for CD34 in both cases (Fig. 3g and 4g). The tumor cells showed characteristic negativity for integrase interactor-1 (INI1), while INI1 positive expression of vascular endothelial

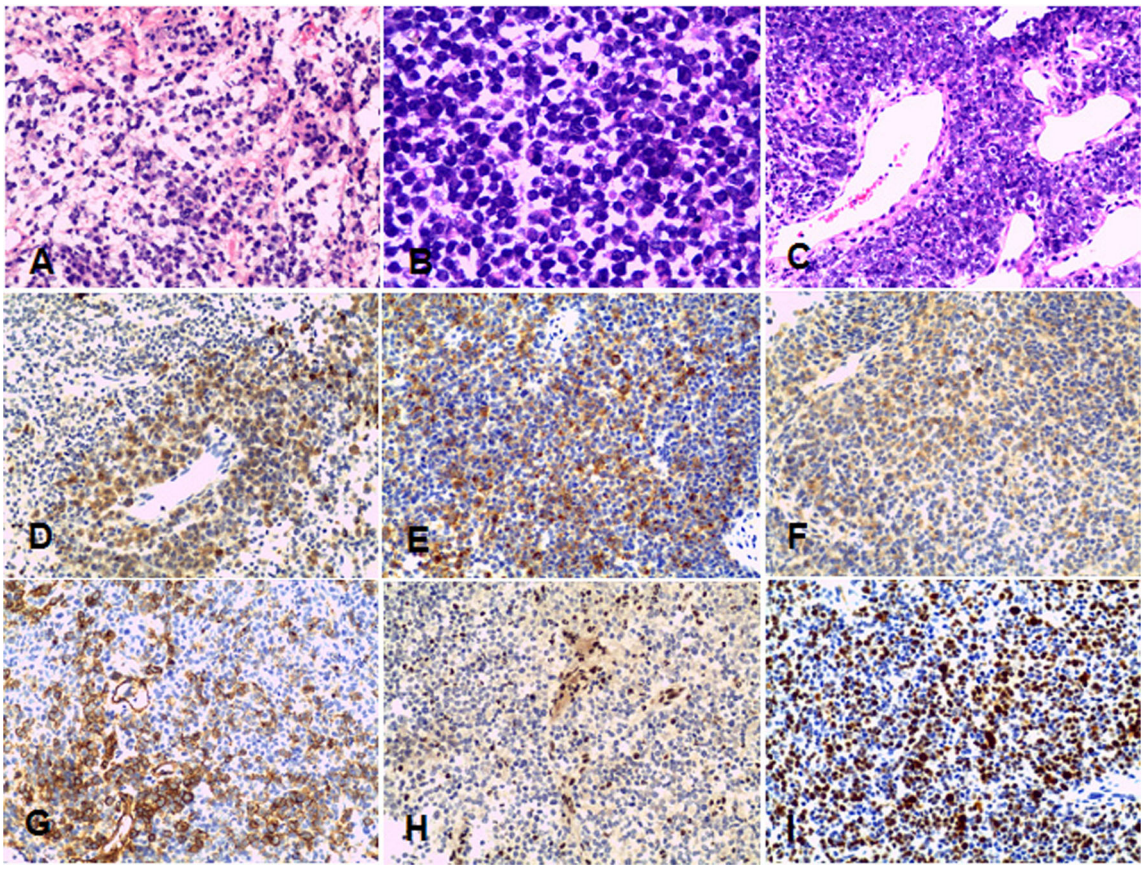

Fig. 3 Histological and immunophenotype of case 1. In the frozen section, proliferative tumor cells were large, abundant cytoplasm, big and atypia nucleus, some cells showed obvious nucleoli. Common mitotic activity was present (**a**). Microscopically, the tumor cells consisted with the atypical epithelial cells and rhabdoid cells (**a**). Some of tumor cells around blood vessels were similar to haemangiopericytoma (**c**). Frequent mitotic activity was present. Majority cells were positive of CK and EMA (**d** and **e**). Syn was weakly positive (**f**). About 20% tumor cells expression of CD34 (**g**). Tumor lacking nuclear expression for INI1 protein; note strong internal positive control staining by endothelial cells (**h**). The MIB-1 proliferation index was high approximately 50% (**i**)

as a positive internal control (Fig. 3h and 4h). About 30% tumor cells express CK 19 in case 1, but negative in case 2. Also, various proportions of tumors expressed CK8 and CK8/18 in both cases. A small number of tumor cells (<5% tumor cells) expressed CD56 in both cases. TP53 positive cells were found (>50%) in the two cases. The MIB-1 proliferation index was higher up to 50–70% (Fig. 3i and 4i). Reticulocyte staining showed abundant intercellular reticular fibers. Myogenic markers (such as, smooth muscle actin (SMA), Desmin, Myoglobin, MyoD1, Myogenin) were negative, but in the case 2, about 5% tumor cells were positive for Actin. The pituitary hormones (such as, growth hormone, prolactin, thyrotropin, ACTH and gonadotropin) were all negative. There was no staining for HMB45, MelanA, NSE, S-100, GFAP, Olig-2, MAP2, CgA, CK5/6, CK7, CK20, P63 and CD31.

Fluorescence In Situ Hybridization (FISH) for INI1 (22q11.2)

Fluorescence in situ hybridization (FISH) was performed in both cases, as previously described [15]. Briefly, 4-mm slides from the formalin-fixed, paraffin-embedded tissue blocks were deparaffinized before hybridization. Dual-color FISH were performed using TUPLE1/ARSA (Vysis/Abbott Molecular) for loss INI-1 (22q11.2). Non-neoplastic brain controls (temporal lobectomy specimens for seizure control) showed 2 red and 2 green signals (TUPLE1/ARSA) in 85% to 90% of the nuclei. Based on these controls, the two cases were considered of deletion for 22q11.2 when there were greater than 30% of tumor cell nuclei harbored 1 red (22q11.2) signal and 1 green (22q13.1–13.3) signal. The results of FISH showed the monoallelic deletions of INI1 in the two cases (Fig. 5a, b).

Pathological Diagnosis

Immunohistochemistry profiles showed that tumor cells with both epithelial and mesenchymal phenotypes, expressed AE1/AE3, EMA, and Vimentin. Tumor cells were positive for CD34 and negative for INI1. FISH results showed monoallelic deletions of INI1 in the two cases. Considering all the information, the two cases should be diagnosed as PES.

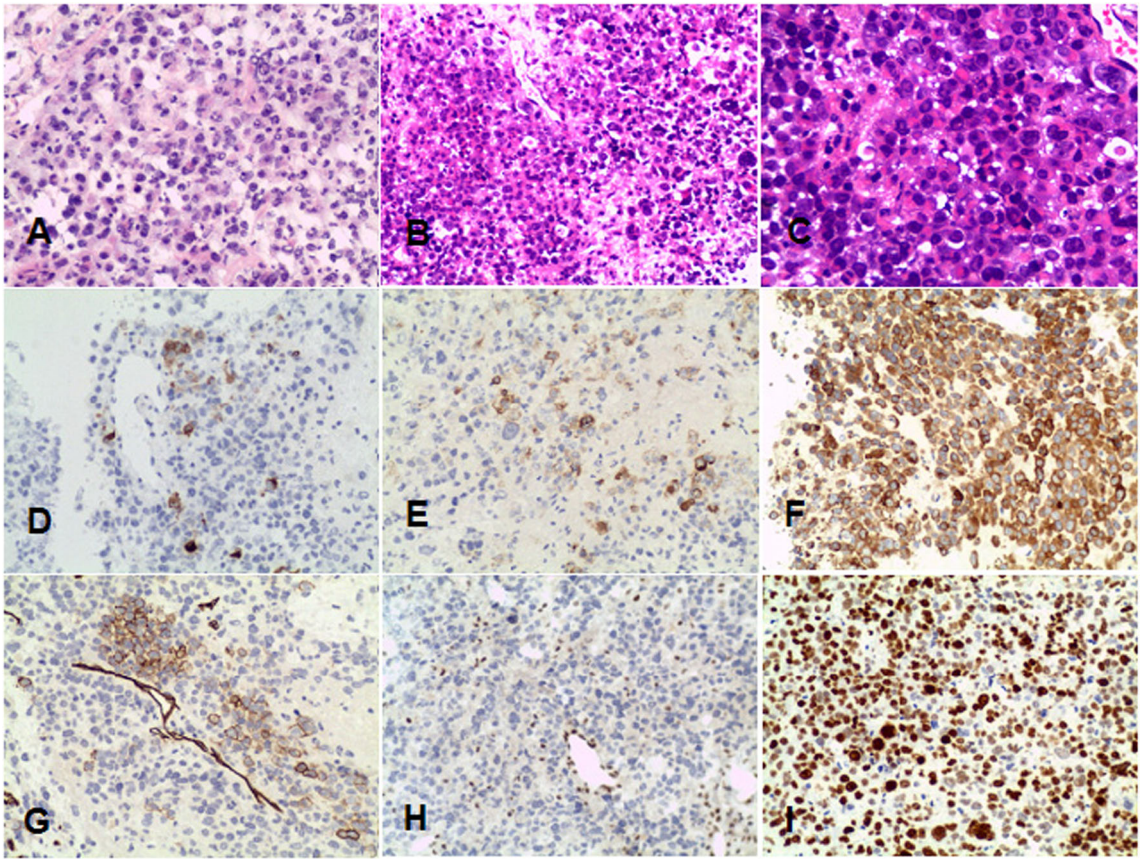

Fig. 4 Histological and immunophenotype of case 2. In the frozen section, tumor cells were large, abundant cytoplasm, big and atypia nucleus, similar to rhabdoid tumors. And, common mitotic activity was present (**a**). Microscopically, atypia tumor cells scattered, seen some expansion of thin-walled blood vessels (**b**). Most of the tumor cells were rhabdoid-like with eccentrically placed nuclei, eosinophilic cytoplasm, and intracytoplasmic, paranuclear hyaline inclusions were seen (**c**). Frequent mitotic activity was present. Small part tumor cells were positive of CK and EMA (**d** and **e**). Syn was strong positive (**f**). About 10% tumor cells expression of CD34 (**g**). Tumor lacking nuclear expression for INI1 protein; note strong internal positive control staining by endothelial cells (**h**). The MIB-1 proliferation index was high approximately 70% (**i**)

Treatment and Follow-Up

Case1 was performed systemic examinations, including CT scans of the chest, abdomen and pelvis, and no abnormalities were found. Case2 had performed PET-CT which demonstrated no metastases. So, the two cases all have primary tumors of the middle cranial fossa. They did not take additional treatment after surgery. Case 1 died less than a month later. Case 2 died half a month after surgery.

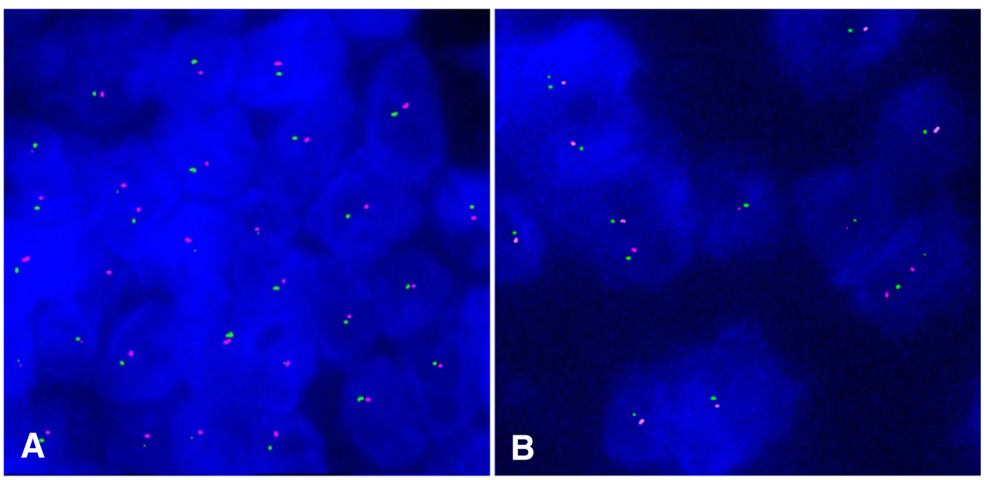

Fig. 5 Fluorescence in situ hybridization (FISH) was carried on the two cases (**a**, **b**). Dual-labeled probe, TUPLE1/ARSA (22q11.2/22q13.1–13.3), showing only one red (22q11.2) and green (22q13.1–13.3) signal in the two cases, indicated the monoallelic deletions of INI1 (22q11.2)

Discussion

Since 1997 the Guillou et al. firstly proposed and named PES, and the diagnosis of PES has been widely accepted [4]. It is a rare, undifferentiated soft-tissue sarcomas. PES affected middle-aged patients and often occured in the proximal and deep-seated locations, sunch as, pelvis, perineum, and genital tract [4, 6–14]. To date, only one case of PES in the skull base has been reported which occurred in a 55-year old Malay man [15]. Therefore, it is worthwhile to report EPS occurred in this location. In this paper, we reported two cases of PES occurred in the middle cranial fossa. They were both middle-aged women, aged 47 and 52 years old respectively. Headache was the main symptom, with or without nausea and vomiting. Cranial nerves involved or pressed resulted in corresponding symptoms, such as optic nerve involvement including vision loss, oculomotor nerve involvement leading to ptosis and visual ghosting. Tumors involved the hypothalamus lead to diabetes insipidus. They can also cause a decline of hormone levels, abnormal body temperature and weight loss.

On clinical and imaging, PES occurred in skull base was easy to be regarded as a primary intracranial neoplasms, such as meningioma, peripheral hemangioma or pituitary adenoma. Case 1 tumor was located in the intrasellar and suprasella, involving the sphenoid sinus. In case 2, the tumor was originally found in the sellar. After the second operation, the tumor was found to be involved in the intrasella and suprasella, butterfly sinus, and the right cavernous sinus. On imaging, invasive pituitary adenoma was the first diagnosis. PES occurred in the cranial fossa especially in saddle area, and it is needed to identify with the most common tumors in this location, particularly invasive pituitary adenoma [16].

Histologically, PES is characterized by a predominantly epithelioid-like tumor cells. It often involved rhabdoid tumor cells. But it was always lack of a granuloma-like pattern as the distal ES [14]. PES has a similar IHC staining profile with the distal ES [10, 14]. It had epithelial and mesenchymal phenotypes with positivity for cytokeratins, EMA and Vimentin [4, 10–12, 14]. CD34 was often positive [4, 10–12, 14]. In some cases, tumor cells express myogenic markers, such as SMA, Actin, Desmin, etc. [4, 10, 14]. In our cases, the tumors were negative for SMA and Desmin, except that some cells were positive for Actin in case 2. In some cases, tumor cells express neuroectodermal related markers, such as, Syn and CD56, while other neuroectodermal related markers were generally negative [10, 11, 14]. Hasegawa et al. [10] reported that about 30% PESs are positive for S-100, but other reports suggested that PESs were generally negative for S100 protein. In our two cases, tumor cells diffusely expressed Syn, and a few tumor cells were positive for CD56.

INI1 (hSNF5/SMARCB1) is a member of the SWI/SNF chromatin remodeling complex located on chromosome 22q11.2 and was constitutively expressed in all cells [17]. It functions as a tumor suppressor gene, controls transcription factors in access to DNA molecules. INI1 deletion was originally discovered in malignant rhabdoid tumors (MRT) of infancy. The mutation or deletion of the INI1 locus at 22q11.2 is the genetic hallmark of atypical teratoid/rhabdoid tumor (AT/RT) [15, 17, 18]. Subsequently, studies found that malignant peripheral nerve sheath tumors (MPNST) also had INI1 deletion [18]. In recent years, INI1 gene deletion was gradually considered to be relatively specific genetic characteristics of ES. More than 90% of ES was reported to loss of INI1 expression [14, 19–24]. Other types of tumors were rarely reported to lose of INI1 expression [23, 25, 26]. In 2008 Hornick et al. [23] conducted immunohistochemistry staining of INI1 protein for 350 tumors, including ES, epithelioid malignant peripheral nerve sheath tumor (MPNT), metastatic tumors, embryonal carcinoma, malignant melanoma and other tumors, with malignant rhabdoid infancy as control. They found that 95% of PES was negative for INI1 protein, 50% epithelioid MPNST and occasional myoepithelial carcinomas are also negative. So the loss of INI1 expression is a typical change of PES [22]. The loss of INI1 protein expression or loss of the INI1 gene can help to confirm the diagnosis of ES. In ES, the loss of INI1 expression may be not only related to the deletion of SMARCB1 gene, but also to epigenetic regulation. Some reported overexpression of miR-206, −381, 671-5p and miR-765 in ES, especially miR-765. It may be used as a diagnostic tool for PES [26]. In the two cases, tumor cells showed characteristic loss of INI1 protein expression. And, FISH showed the monoallelic deletions of INI1. We need further works to detect the expression of these miRNAs.

PES is rare which makes the pathological diagnosis difficult. It need to distinguish from other tumors including epithelioid-like or rhabdoid tumors, such as melanoma, rhabdoid meningioma, epithelioid MPNST, rhabdomyosarcomas, adult AT/RT, angiosarcoma, synovial sarcoma, and poorly differentiated or undifferentiated carcinomas [4]. IHC staining can be helpful to delineate cellular lineages. PES occurred in intracranial needs to distinguish with primary intracranial tumors, especially rhabdoid meningioma, adult AT/RT, and epithelioid MPNSTs, as they have some similar morphological appearances, immunohistochemical profiles and genetic changes.

Meningiomas typically attached to the inner surface of the dura mater as the the common tumors of the skull base. Rhabdoid meningioma is an uncommon type of meningiomas. It predominantly contain sheets of rhabdoid tumor cells, often has high proliferative indices and other malignant histological features, corresponding to WHO grade III [27]. Meningiomas have diverse phenotypes, express Vimentin, EMA, PR, and sometimes are positive for cytokeratins, CD34, S-100, ect. However, INI1 expression has been retained in all meningiomas. Although, some studies reported that about 71% rhabdoid meningiomas showed 22q deletion,

they had no concomitant loss of INI1 expression [28]. It may be useful for differential diagnosis of PES.

AT/RT is a pediatric tumor most often occurred under the age of 3, and rarely in children older than 6 [17]. Occasionally, some cases occurred in adults, and the oldest age was 43 recorded to date [28, 29]. Adult AT/RT was difficult to identify with PES. The loss of INI1 expression and INI1 mutation or deletion are typical characteristics of them. According to our studies, the following clues can help us to identify them. First, PES often occurs in middle-aged people while AT/RT rarely occurs in adults. Second, PES involves the meninges or soft tissue of skull base while AT/RT involves brain parenchyma as central nervous system embryonal tumors [17, 26]. Third, PES is characterized by epithelial-like tumor cells, and is often accompanied by some rhabdomyoid cells. Most AT/RTs contain variable components with primitive neuroectodermal, interstitial and epithelial features except rhabdoid cells [17]. Fourth, PES have epithelial and mesenchymal differentiation, and CD34 is an important immunophenotype. Generally, PES do not express neuroectodermal markers [10, 11]. AT/RTs demonstrate expressions of EMA, SMA and Vimentin. Immunoreactivities for GFAP, NFP, Syn, and cytokeratins are also commonly observed [17].

Epithelioid MPNSTs often have a diffuse expression of S-100, even more common than conventional MPNST, and might be positive for CK and EMA occasionally [17]. MPNT is often accompanied by a variety of genetic abnormalities usually involve 17q (NF1) [30]. Some studies have found about 50% of epithelial MPNSTs presented the loss of INI1 [22, 23]. Although epithelioid MPNSTs also lose INI1 expression as PES, other mmunohistochemical differences can still help to identify them. Eepithelial MPSTs are more inclined to strongly express neural markers, such as S-100, SOX10 and Syn [30, 31]. While PES is generally negative for S-100. And epithelioid MPNSTs generally don't express CD34 [31, 32].

Traditional treatment of ES was wide surgical resection. Radiation and chemotherapy were used as adjuvant therapies. However, the impact of adjuvant therapy on survival of patients was not sure [7, 14, 33–35]. Studies have shown that PES behaved more aggressively than conventional distally located tumors. It has an aggressive clinical course, including distant metastasis and short survival [4, 6, 7, 10, 14, 34]. Only one case of PES in the skull base was reported. We retrieved the patient who underwent tumor resection and revealed no intracranial tumor and spinal drop metastases after one month of surgery by MRI of the brain and spine [15]. After examinations, our two cases were primary PES in the middle cranial fossa without distant metastasis. The prognosis of them were very poor. They died respectively less than one month and half a month after surgery, and had no time to carry on adjuvant radiation and (or) chemotherapy therapy. The overall survival time of them was about three months. The tumor grew rapidly and was easy to infiltrate into the surrounding tissues. And the particular location of the skull base leaded to the difficulty in completing removal of the tumor by surgery and postoperative complications.

Conclusion

PES is rare, undifferentiated soft-tissue sarcomas in adults, with epithelioid features. PES occurred in the skull base are very rare and the pathological diagnosis is very difficult. It is often needed to identify with other mimic tumors, particularly rhabdoid meningioma, adult AT/RT, and epithelioid MPNST. PES behaved more aggressively than distal ES. PES occurred in the skull base was very rare. The tumor grew rapidly and was easy to infiltrate into the surrounding tissues. It may suggest that the prognosis of PES in the base of the skull was even worse than in other sites.

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