CASE REPORT
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Mediastinal metastasis of primary extraneural ependymoma: A case report

Primarni ekstraneuralni ependimom – metastaza u medijastinumu

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Abstract

Introduction. The rarity of primary extraneural ependymomas (EnEs), its great variations in morphology and rare occurrence of metastasis, increase chances of misdiagnosis, particularly if they are found in paraovarian localization. **Case report.** The presented patient was diagnosed with malignant mesothelioma 14 years ago, after right salpingo-oophorectomy. In following years patient had multiple and extensive surgical procedures, resulting in different histopathological diagnoses, and after seven years, a diagnosis of EnE was established. Later on, patient was surgically treated in several medical centers across the region, again with different histopathological diagnoses. At present, the tumor metastasized to mediastinum, presenting as a grey to brown, multicystic formation with cysts filled with a clear serous fluid or red-brown hemorrhagic fluid. The inner surface of the cysts had smooth to partly papillary appearance. Tumor cells exhibited several architectural patterns (solid, pseudorosette or rosette formations, papillary and pseudopapilary structures), and immunophenotype specific for EnE [glial fibrillary acidic protein (GFAP), estrogen receptor (ER), and progesterone receptor (PR) positive; calretinin, WT-1, S100, synaptophysin, chromogranin, CK7 and pan-cytokeratin negative]. **Conclusion.** This case demonstrates not only specific diagnostic immunophenotype of extraneural ependymoma, but above all an important principle in tumor pathology. Rare neoplasms may occur in unusual and unexpected primary and metastatic sites. Pathologists need to be familiar with histologic features of a wide range of neoplasms and not just the appearance of neoplasms within their own limited subspecialty area.

Key words:
ependymoma; central nervous system neoplasms; diagnosis; histological techniques; immunohistochemistry; mediastinal neoplasms; neoplasm metastasis.

Apstrakt

Uvod. Osnovni razlog čestih grešaka u dijagnostikovanju ekstraneuralnih ependimoma (EnE), posebno onih lokalizovanih u paraovarijalnoj regiji, jesu njihova niska incidencija, velike varijacije u histomorfološkim odlikama i retka pojava metastaza. **Prikaz bolesnika.** Prikazana je bolesnica kojoj je maligni mezoteliom dijagnostikovan 14 godina ranije, posle desne adneksetomije. Narednih godina, bolesnica je bila podvrgnuta nisu operativnih zahvata u bolnicama u matičnoj državi i u regionu, a na osnovu pregledanog materijala postavljeno je nekoliko različitih patohistoloških dijagnoza. Dijagnoza EnE prvi put je postavljena 7 godina ranije, a posle je postavljeno još nekoliko patohistoloških dijagnoza, bez odgovarajućih analiza u pravcu potvrde ependimoma. Po prijemu u našu ustanovu, bolesnici je konstatovano prisustvo lobulirane promene u medijastinumu, koja je makroskopski bila sivkasto-mrke boje, multicistična. Ciste su bile ispunjene bistro-seroznim do hemoragičnim tečnim sadržajem. Unutrašnjost cisti bila je glatka i delom papilarnog izgleda. Histološki, tumorske ćelije su bile aranžirane u solidne, papilarne i pseudopapilarne formacije, a fokalno su se formirale rozete. Imunofenotip tumorskih ćelija odgovarao je karakteristikama EnE [glijalni kiseli fibrilarni protein (GFAP), estrogenski receptor (ER), progesteronski receptor

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(PR) pozitivne; kalretinin, WT-1, S100, sinaptofizin, Ovaj slučaj ne ilustruje samo specifični dijagnostički imunofenotip ekstraneuralnih ependimoma, već, pre svega, ističe važan princip u tumorskoj patologiji. Retke neoplazme, bilo primarne ili metastatske, mogu se javiti na neuobičajenim i neočekivanim lokalizacijama. Patolozi moraju biti upoznati sa histološkim osobinama širokog hromogranin, CK7 i pan-citokeratin negativne]. **Zaključak**. spektra neoplazmi i to ne samo iz njihovog užeg polja rada.

Ključne reči:
ependimom; nervni sistem, centralni , neoplazme; dijagnoza; histološke tehnike; imunoistohemija; medijastinum, neoplazme; neoplazme, metastaze.

Introduction

Typical ependymomas are rare neuroepithelial tumors originating from the glial ependymal cells of the central nervous system (CNS). A vast majority of ependymomas occurring in adults are localized in the ventricles and spinal cord. Rarely, they occur outside the CNS [extraneural ependymomas (EnEs)], and even than mostly in close relationship with neural axis. The majority of primary EnEs are seen in the sacrococcygeal subcutaneous tissue and paraovarian area, but they have also been reported in the extraovarian pelvic region and more infrequently in other sites [1–4].

We reported the case of a female patient presenting with a mediastinal metastatic deposit of primary EnE.

Case report

A female patient, aged 41, was admitted to the Institute for Pulmonary Diseases of Vojvodina, Sremska Kamenica, Vojvodina due to a mediastinal tumor. Since the patient was a foreign national, initially treated in her country and other regional hospitals, the medical documentation was incomplete, and document of histopathological examination was not available.

The patient gave anamnestic data that her initial surgical procedure was right adnexetomy and reduction of tumor mass in pelvic cavity 14 years ago (when she was 27 years old), with histopathological diagnosis of poorly differentiated malignant mesothelioma. Postoperatively, the patient was treated with combined chemoterapy [docetaxel/cisplatin (CDDP) protocol].

At the age of 29, the left ovary cyst was removed, histopathologically diagnosed as a cyst of germinal epithelium, followed by chemotherapy [cisplatin/etoposide/bleomycin (PEB) protocol].

According to patient's anamnesis, at the age of 34, "pseudocyst" from pelvic cavity was removed, and histopathologically diagnosed as well differentiated ependymoma.

At the age of 36, tumorectomy of the left ovary mass and appendectomy were performed, with pathology-confirmed ependymoma metastasizing to the appendix. In the same year, due to multiple metastases, the patient underwent extensive surgery: left adnexectomy, rectosigmoid resection by the Hartmann's procedure, resection of terminal ileum and cecum, right hepatectomy, cholecystectomy, retroperitoneal lympadenectomy, omentectomy, partial peritonectomy, resection of the right hemidiaphragm and tumorectomy for right pleural mass. Chemotherapy (etoposid) was applied postoperatively.

Fine needle aspiration (FNA) of inguinal lymph nodes was performed a year later, at the age of 37, with histopathologically confirmed only reactive changes in lymph nodes. Positron emission tomography/computed tomography (PET/CT) scans in 2014 revealed suspicious lymph nodes near internal mammary artery, which were sampled during video-assisted thoracoscopic surgery (VATS), with pathologically evident tumor metastases. At that time, tumor tissue was composed of medium sized atypical cells, with oval hyperchromatic nuclei, and focally prominent nucleoli. Immunohistochemical analysis showed alpha fetoprotein (AFP) and D2-40 to be positive in all tumor cells; CD30, placental alkaline phosphatase (PLAP) and CK19 were negative. Based on this immunofenotype, diagnosis of metastatic germ cell tumor was set.

Suspicious cystic mediastinal lesion was observed at PET/CT at the age of 40 (2016), and in control PET/CT in next year (2017), somewhat elevated activity/fluoro-deoxyglucose (FDG) accumulation [maximum standard unit value (SUVmax) = 1.7] was observed in the left paracardial area (all imaging analyses were done abroad, and images were not available to us after the patient was sent home). After adequate preoperative procedures, VATS was used to identify and extirpate cystic lesion loosely attached to mediastinum, diaphragm and pericardium, while phrenic nerve was passing over the lesion. Material was sent to histopathological analysis. The post-operative recovery was unremarkable, and the patient was discharged four days later.

Histopathological findings

Material sent for histopathological analysis was grey to brown tissue, lobulated and cystic in its macroscopic appearance, 8×4×2.5 cm large. On cross sections it was multicystic, with cysts filled with clear serous fluid or red-brown hemorrhagic fluid. The inner surface of the cysts had smooth to partly rough and papillary appearance.

Histological slides stained with hematoxylin and eosin (HE) revealed cystic tumor composed of oval, spindle to polygonal tumor cells, with scant clear or light eosinophilic cytoplasm (Figure 1). Nuclei were oval, round and spindle shaped, hyperchromatic, with marked pleomorphism and atypia. Some nuclei had granular chromatin ("salt &

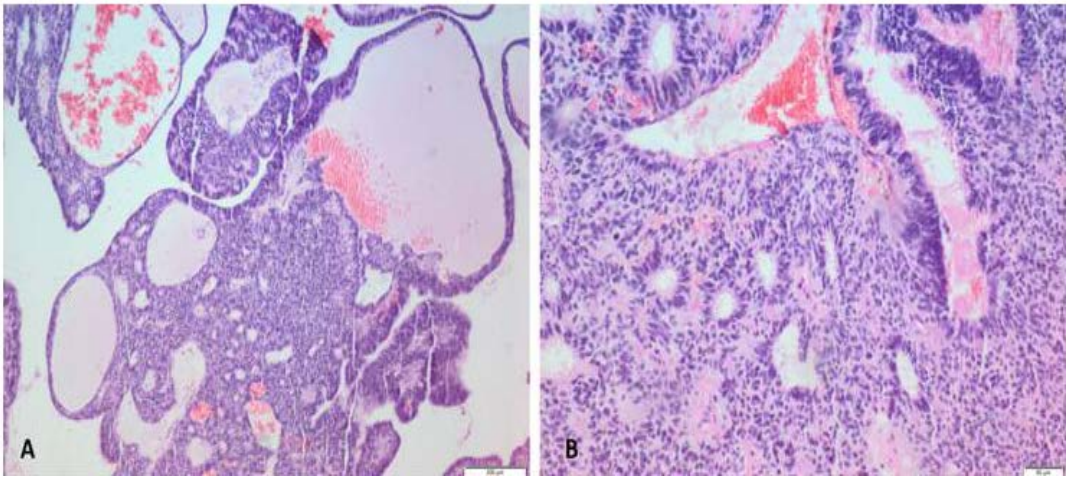

Fig. 1– Photomicrographs of the tumor tissue: A – solid and cystic areas; cysts filled with eosinophilic amorphous material and erythrocytes (HE, 40×); B – oval, spindle and polygonal tumor cells, with scant clear or light eosinophilic cytoplasm, with pseudorosette or rosette formations (HE, 100×).

pepper"). Mitoses were rarely present (2 per 10 high power fields). Cell borders were poorly defined. Tumor cells exhibited different architectural patterns: solid, pseudorosette or rosette formations, papillary and pseudopapilary stuctures. Cystic spaces were filled with eosinophilic amorphous material and erythrocytes. Neither necrosis nor vascular invasion were observed. Based on patient's anamnestic data and histological appearance of the tumor, additional immunohistochemical analysis was indicated. Tumor cells showed strong glial fibrillary acidic protein (GFAP) immunoreactivity, as well as estrogen receptor (ER) and progesterone receptor (PR) immunoreactivity (Figure 2). Less than 5% of cells showed positive Ki-67 nuclear staining (Figure 2). Tumor cells were negative for calretinin, WT-1, S100, synaptophysin, chromogranin, CK7 and pan-cytokeratin staining.

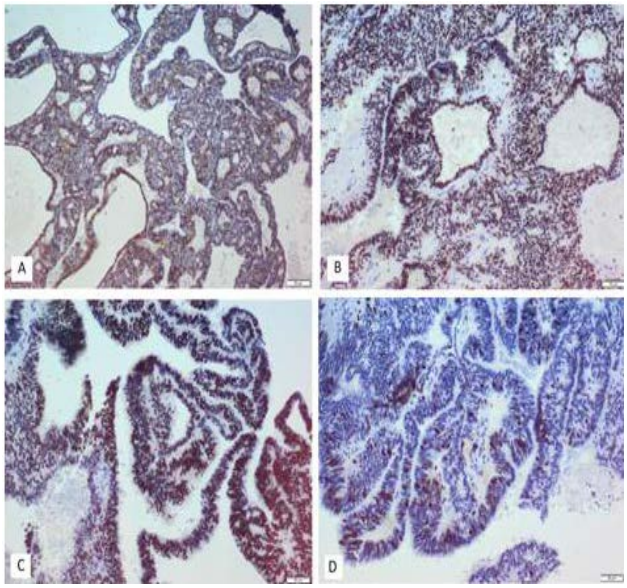

Fig. 2 – Immunophenotype of the tumor: A – GFAP, 40×; B – ER, 100×; C – PR, 100×; D – Ki67, 100×. GFAP – glial fibrillary acidic protein; ER – estrogen receptor; PR – progesteron receptor.

Discussion

Typical ependymomas behave in an indolent, slow-growing manner. While generally behaving in a benign clinical fashion, they possess capacity for localized tumor recurrence and tumor dissemination trough cerebrospinal fluid with metastases has been known to occur [5]. EnE appears to behave in a similar fashion, but there is a potential for malignant clinical behavior, although it appears to be an uncommon occurrence [5]. In presented case, onset of the disease was 14 years ago, and since that time, the patient has had multiple and extensive surgical procedures, due to metastatic spread.

While sacrococcygeal ependymomas are equally distributed among males and females, paraovarian pelvic and extra pelvic ependymomas have been exclusively reported in women, mainly of child bearing age [1, 3]. However, there was a case of a 75-year-old patient with pelvic EnE [5]. This reported gender and age related predominance is supported by numerous case reports, and is in accordance with our patient's gender and age. Initially, her disease was diagnosed when she was 27 years old, but at that time, the diagnosis was malignant mesothelioma. Since we do not have medical reports and histological slides, we can only doubt that it was also an EnE. Similar case was described by Verdun and Owen [5]: a female patient operated for upper right quadrant tumor, presumed to be metastatic pancreatic tumor, but postoperatively diagnosed as mesothelioma. Two years later, the patients developed recurrent tumor that was localized in pelvic region. At that time, tumor samples were reviewed and with the aid of immunohistochemistry, the diagnosis was corrected to EnE.

Ependimomas of CNS have distinct histology characterized by perivascular pseudorosettes, true ependymal rosettes, and fibrillary areas. In contrast, primary EnE have been described as having a wider range of microscopic architecture: perivascular pseudorosettes and occasionally true ependymal rosettes, along with mixtures of solid,

macrocystic, microcystic, pseudopapillary, papillary, trabecular, and cribriform architectures [3].

It is observed that EnE and ependimomas of CNS beside different clinicopathologic features, differ in immunophenotypical features as well. It may point to either a derivation from different precursors or differentiation along different pathways [6]. Different origin and development, immunophenotipical features and highly variable histology of EnE is at the same time a cause of many diagnostic errors [4].

The EnE are thought to be derived from embryonal rests in the paracoccygeal area, but there is also hypothesis that the pelvic ones might be arising from ectopic glial cells or might be neometaplasia of the peritoneal mesenchymal tissue [1, 5]. Another hypothesis proposes that some extraspinal ependymomas arise from germ cells and germ cell tumors (teratomas) and may therefore account for ependymomas arising in the ovary, parametrium, and anterior mediastinum [6, 7].

Idowu et al. [6] studied and compared primary CNS ependymomas EnE. Although both types stain positive for GFAP, they found several immunohistochemical differences, with EnE most likely positive for cytokeratins: 34betaE12 (60% vs. 0%), CK18 (100% vs. 20%), CAM 5.2 (60% vs. 10%), CK7 (80% vs. 10%). ER and PR are also strongly and diffusely positive in a majority of EnE compared with CNS ependymomas (ER: 100% vs. 10%; PR: 80% vs. 20%, respectively) that show weak and focal staining for these receptors in a minority of cases. CD99 and S100 are more commonly positive in CNS ependymomas than in their extraneural counterparts. This immunophenotype stated by Idowu et al. [6] is present in all published cases of EnEs [3–5], and it confirms the hypothesis that EnEs arise by different mechanisms from their CNS counterparts [6]. However, it appears that EnEs arising in different place or mechanism, show different immunoprofile. A case of ependymoma arising from mature cystic teratoma was published by Stolnicu et al. [4] and it showed immunofenotype of EnE, but it was markedly different from other EnEs.

In our case, ovaries were affected by the disease, and on one occasion even diagnosed as AFP positive germ cell tumor. Similar case was presented by Garcia-Barriola et al. [8], when a 30-year-old woman was given an erroneous diagnosis of poorly differentiated carcinoma of the ovary. The patient presented pelvic pain for one year prior to surgery. A second laparotomy revealed a bilateral pure ovarian ependymoma that infiltrated the uterus and presented implants on the omentum. Differential diagnosis included mainly endometrioid and small cell carcinoma of the ovary, but presence of typical ependymal rosettes and positivity to GFAP confirmed the diagnosis of ependymoma [8]. Data on AFP expression in EnE are rare, precisely we have found only one case mentioning negative AFP expression in pelvic EnE [4]. This may be the cause for debate on origin of the primary tumor, but it also emphasizes the importance of comprehensive and thorough differential diagnostic in cases of ovarian lesions. Chances of misdiagnosing EnEs of ovarian localization are high, particulary since they may show papillary areas with psammoma bodies, pseudofollicles, trabeculae, microcysts and other patterns resembling *struma ovarii*, granulose cell, Sertoli-Leydig cell, serous and Wolffian tumors [4, 9]. Therefore, diagnoses made at the age of 29 (cyst with granulosa cells) and the age of 38 (metastatic germ cell tumor) could be questioned.

We were able to do some additional immunohistochemistry on the tissue sample diagnosed as AFP positive germ cell tumor metastasis, so we applied GFAP staining. Tumor tissue showed moderate GFAP positivity, which confirmed our suspicions regarding the previous diagnosis. Indeed, it was a metastasis of primary, AFP positive EnE.

Besides differentiating primary neural from EnE, metastatic carcinoids and primitive neuroectodermal tumor should be considered as differential. As EnEs can appear in liver, lung, small intestine, omentum and even endometrium, this entity should also be kept in mind in the differential diagnosis of a primary or metastatic carcinoma with papillary or pseudopapillary structures. Although our case was not positive with any of the keratin antibodies, it should be borne in mind that ependymomas may express cytokeratins and may be misdiagnosed as metastatic carcinoma. In such cases if the morphologic pattern raises suspicion to EnE, GFAP staining will be a helpful diagnostic tool [1, 10].

Conclusion

This case demonstrates not only diagnostic immunophenotype of EnE, but above all an important principle in tumor pathology. Neoplasms may rarely occur in unusual and unexpected primary and metastatic sites. Pathologists need to be familiar with histologic features of a wide range of neoplasms and not just the appearance of neoplasms within their own limited subspecialty area. Correct diagnosis may be achieved by tumor pattern recognition on initial routine slides followed up by confirmatory immunostains.

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