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Review and Case Report

Prescapular primitive neuroectodermal tumor – review and case presentation

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Abstract. Primitive neuroectodermal tumors represent a distinct group of rare malignancies, which develop from small round cells that belong to soft tissue or bone tissue. Peripheral neuroendocrine tumors are histologically difficult to differentiate from other small round cell neoplasms such as extra-Ewing sarcoma, embryonic rhabdomyosarcoma, neuroblastoma or lymphoma. A female patent, 72 years old, from the rural environment, presents in the ambulatory service for pain at the scapular and subscapular level on the right side. From the paraclinical point of view, complete hemolithogram, liver, kidney, ionogram, plain chest radiography, contrast MRI were performed preoperatively. The surgical intervention with complete excision of the tumor and histopathological examination was accomplished. The histological appearance advocates for a primitive neuroectodermal tumor. Due to their aggressive nature and low incidence, primitive peripheral neuroectodermal tumors are challenging to manage for the clinician and require a multimodal approach that combines surgery, chemotherapy and radiotherapy. The difficulty of evaluating patients with primitive peripheral neuroectodermal tumours lies in the small number of cases reported in literature and insufficient data from obtained large scale studies.

Key Words: neuroectodermal tumor, sugery.

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Introduction

Primitive neuroectodermal tumors represent a distinct group of rare malignancies developed from small round cells, which belong to soft or bone tissue. They evolve from the level of the embryonic neural crest, most likely through cell migration. Peripheral neuroectodermal tumors account for about 4% of the total connective tissue neoplasms and occur most commonly in children, adolescents and young adults up to 25 years old, males and Caucasians are more frequently affected (Dchner et al 1993, Coffin et al 1989).

Neuroectodermal tumors were first described in literature in 1935 by Stout and in 1979 by Askin et al. (1979) as "small cell malignancies of the thoracic pulmonary region" - (Askin tumor) of neuroectodermal origin. Tumors with similar characteristics were subsequently observed in the retroperitoneum, pelvis, extremities and other sites. These tumors were classified as a distinct entity in 1984 by Jeff et al (Jaffe et al 1984).

According to the World Health Organization, primitive peripheral neuroectodermal tumors, classic Ewing's sarcoma, and extracellular Ewing sarcomas are the family of Ewing's sarcomas. Primitive neuroectodermal tumors are a variant of small, malignant, aggressive round cells with low differentiation. From the histological point of view, these have been described as round, small cells with dark spots, which possess hyperchromatic nuclei with a high mitotic rate (Cavazzana et al 1985).

Peripheral neuroendocrine tumors are histologically difficult to differentiate from other types of small round cell neoplasms such as extra-Ewing sarcoma, embryonic rhabdomyosarcoma, neuroblastoma or lymphoma. The diagnosis can be established through immunohistochemistry and also by electron microscopy, methods that can demonstrate the different degrees of neural differentiation. (Steiner et al 1989, Seemayer et al 1975) The distinction between small cell neuroectodermal tumors and other small cell neoplasms, in particular Ewing's sarcoma and neuroblastoma, is based on the demonstration of neurosecretory granules by electron microscopy and using immunohistochemical and cytogenetic methods that will define their specific characteristics. Neural markers such as neuron-specific enolase-positive staining are generally observed in peripheral primitive neuroectodermal tumors and neuroblastoma, in comparison to Ewing sarcomas, where they are not observed, on the ohter hand PAS (periodic acid-Schiff) staining reacts with Ewing's sarcoma cells and rarely with perimeter and neuroectodermal tumors. Additional neural markers are synaptophysin, chromogranin, neurofilaments protein S-100 and vimentin. These features along with antigen patterns defined by different monoclonal antibodies place primitive peripheral neuroectodermal tumors between neuroblastoma and Ewing's sarcoma, demonstrating features of both entities (Triche et al 1983, Reynolds et al 1985, Donner et al 1985).

The presence of rosettes, especially the typical Homer-Wright rosettes, indicates neural differentiation and aids in the diagnosis of peripheral primitive neuroectodermal tumor. Immunohistochemistry points 90-100% expression of CD99 gene, with chromosomal translocation t (11;22) (q24;Q12) (Zhang etal 2011). The positive expression of at least two neural markers and/or the presence of Homer-Wright rosettes is mandatory for the positive diagnosis of primitive peripheral neuroectodermal tumor (Gao et al 2019). The current incidence of peripheral primitive neuroectodermal tumors is difficult to assess due to the low incidence. Most of the studies in literature are represented by case studies and the positive diagnostic criteria have only recently been defined (Kalantari et al 2015). The estimated incidence is about 2.9 / million inhabitants/ year (Ghosh et al 2009). Due to the rare occurrence of these tumors, radiological diagnosis can be difficult. Compared to the morphopathological diagnosis, CT and MRI are non-invasive investigations that can provide preoperative details on the location, morphology, size and margin of the tumor, as well as its vascularization and any secondary determinations. Although in some cases CT and MRI may also provide information on the histopathological nature of the tumor, with some specific imaging features, these have only been sporadically studied in the literature and cannot establish a positive diagnosis in this regard. There are no clear treatment guidelines established for peripheral primitive neuroectodermal tumors. The surgery represented by the total excision of the tumor together with the neo- and adjuvant chemotherapy and the adjuvant radiotherapy represents the primary treatment of this pathology. Despite numerous treatment methods, primitive peripheral neuroectodermal tumors are aggressive neoplasms and have a reserved prognostic (Tan et al 2014).

Case presentation

Female patient, 72 years old, pensioner, from rural environment presents in our ambulatory service for a right subscapular mass and pain at the scapular and subscapular level on the right side, with dull character, which started about 2 years ago.

From the personal medical history, it is worth mentioning hypertension stage III, with high additional risk and osteoporosis.

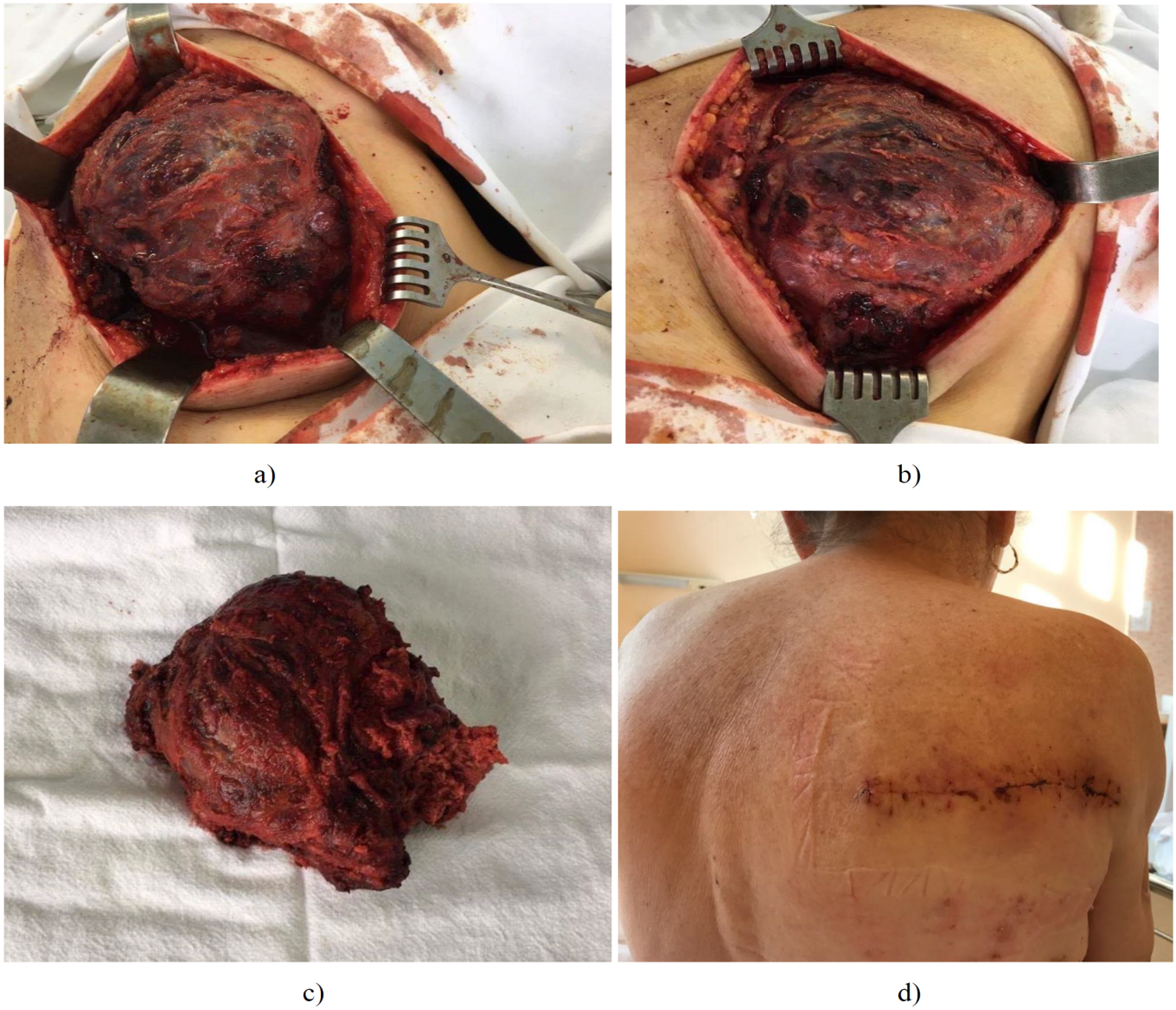

Figure 1. a) and b) Intraoperative images of the tumor. c) Macroscopic appearance of the tumor after surgery. d) The final postoperative appearance of the region

Family history, living and working conditions are not bring no additional information.

At the clinical examination, we noticed an oval tumor of 100/71 mm in diameter, painful on palpation, immobile compared to the adjacent plans.

From the paraclinical point of view, the complete hemolithogram, liver, kidney, ionogram, plain chest radiography, contrast MRI were performed preoperatively. Mild hypocalcemia and increased LDH could be distinguished. MRI examinations observed with dimensions of 104/70 / 60 mm, with infiltrative contour, in T1 isosemnal and T2 heterosignal, with diffusion restriction on DWI sequences, with necrosis areas included, extension at the level of the supraspinous, infraspineous, subscapular and trapezius muscles, which lack the scapular within the inner third. On the STIR sequences, bone edema is highlighted. At axillary level, lymphonodular images are highlighted. No lesions are detected in the pulmonary hemicampus included in the examination. The pulmonary and chest X-ray, an asymmetrical chest, subcutaneous sclerosis, opaque aorta and free SCD are detected.

The surgical intervention consisted of complete excision of the tumor with consecutive histopathological examination. It was undergone under spinal anesthesia and the tumor is with R0 macroscopic margins. Postoperative evolution is favorable under antibiotic (Ciprofloxacin, Ceftriaxone, Gentamicin), anti-inflammatory (Dexamethasone), antialgic (Algocalmin, Ketoprofen, Fentanyl, Mialgin, Paracetamol.), anticoagulant (Clexane) treatment, hydroelectrolytic balance (Ringer, Glucose 5%).

The pathological result shows malignant tumor proliferation consisting of small and medium sized cells, uniform, superimposed, with indistinguishable cell boundaries, round /oval nuclei, finely dispersed chromatin, small nucleoli and eosinophilic cytoplasm. Tumor cells are predominantly perivascular, with extensive areas of necrosis (70%) and neutrophilic inflammatory infiltrate. Tumor proliferation infiltrates adipose tissue and adjacent skeletal muscle mass and reaching surgical resection margins. Special colors: PAS negative, Gomori - highlights reticulin in the vessels; the coloration is negative, which supports the diagnosis of PNET. Immunohistochemical profile reveals CD-99 and positive vein, ki-67 positive on 70% of cells. The appearance advocates for a primitive neuroectodermal tumor pT2bNx L1V1R1.

Discussion

Primitive peripheral neuroectodermal tumors are rare type of malignancies with low prevalence even in large oncological centers, where more than 6 cases per year are rarely reported

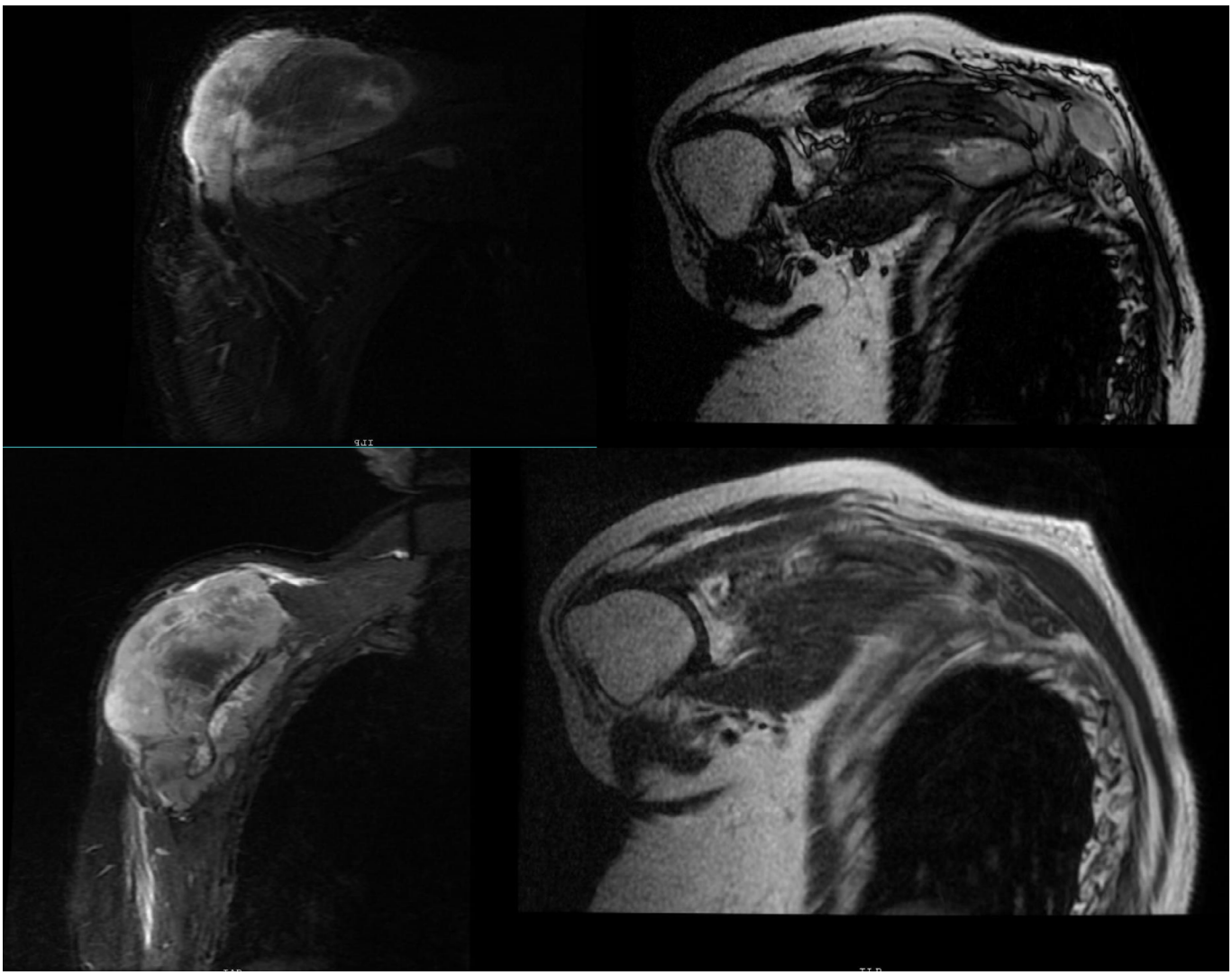

Figure 2. MRI images of the right scapular tumor

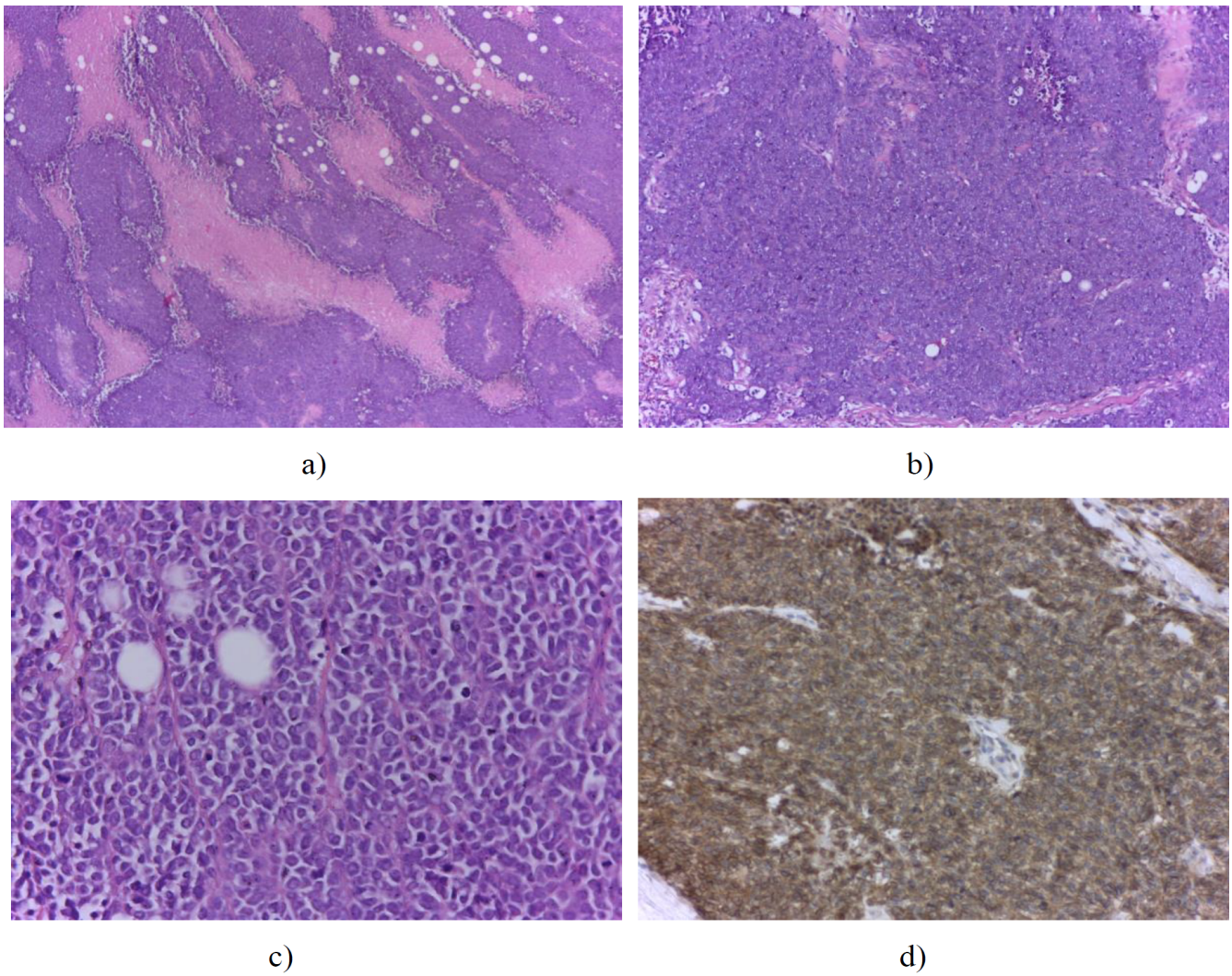

Figure 3. a), b), c) The image shows tumor cells predominantly perivascular, with extensive areas of necrosis and neutrophilic inflammatory infiltrate. Tumor proliferation infiltrates adipose tissue and adjacent skeletal muscle striated muscle tissue. d) Special colorings - Gomori - highlights the reticulin in the vessels; the coloration is negative intratumoral, which supports the diagnosis of prescapular primitive neuroectodermal tumor

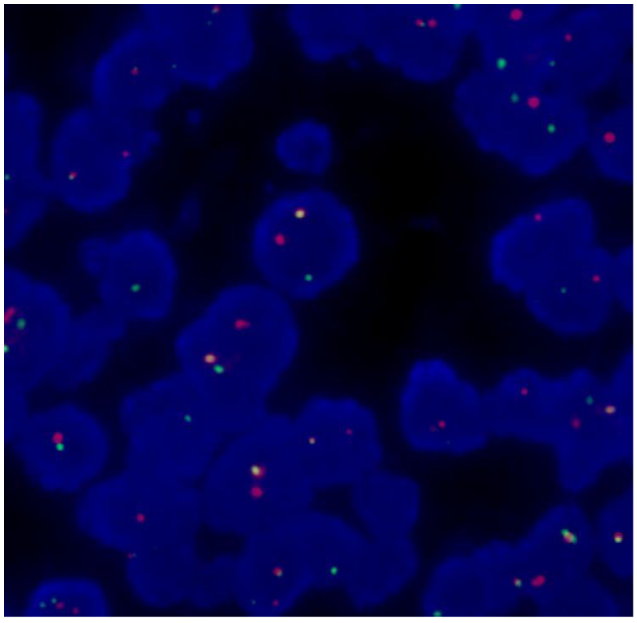

Figure 4. FISH examination using Vysis EWSR1 Break Apart FISH Probe showing in the center two non-overlapping nuclei presenting one fusion, one red, and one green signal pattern

(Kimber et al 1998, Fukumoto et al 1997, Marina et al 1989, Schmidt et al 1985). This pathology affects all age groups, but is more common in adolescents and young adults. The age of the patients in the specialty literature is between 1 and 73 years. According to Enzinger and Weiss, primitive peripheral neuroectodermal tumors are more common in adults, with the exception of Askin tumors, with an age range of 2 to 43 years and an average of 21 years (Enzinger et al 1983). A male predominance has been described in most of the studies (Schmidt et al 1991, Schmidt et al 1983, Jürgens et al 1988, Llombart-Bosch et al 1989, Marina et al 1989, Kushner et al 1991, Jones et al 1995, Zimmermann et al 2001, Thyavihally et al 2008, Demir et al 2009, Biswas et al 2013, Sirivella et al 2013, Tan et al 2014, Yi et al 2017).

The most commonly encountered sites were the trunk including the thoracic wall, especially the posterior one and the paravertebral region (50% -60%), the thorax-pulmonary region - Askin tumors (40%) and the extremities (20% -25%) (Ibarburen et al 1996).

Patients are generally admitted in hospital accusing a painful tumor mass with or without paraneoplastic symptoms. The natural progression of the disease is to exitus in 70% of the cases

in the first three years after the diagnosis, due to the secondary determinations. In a study by Schmidt et. co, the survival rate for patients with primitive peripheral neuroectodermal tumors at 7.5 years was 40% (Schmidt et al 1991). Jurgens et al (1988) demonstrates a survival of 56% at 3 years after diagnosis for non-metastatic patients and denies curative treatment for metastatic patients. Comparison of survival rates in patients with primitive peripheral neuroectodermal tumors is difficult due to sporadic tumor frequency and age heterogeneity. In general, these patients have a poor prognosis with a survival rate below 40%, despite any treatment method applied. Some studies even report a 90% mortality rate at 3 years (Hashimoto et al 1983, Enzinger 1983).

A substantial number of patients present to the doctor in the metastatic stage of the disease (Hashimoto et al 1983, Schmidt et al 1985, Llombart-Bosch et al 1989, Marina et al 1989, Jones et al 1995, Ibarburen et al 1996, Biswas et al 2013). Metastasis occurs most commonly in bone and lung level (Ibarburen et al 1996, Askin et al 1979, Miser et al 1985, Fink et al 1985). A study by Liming et al. in 2019 shows a survival rate of patients in metastatic stage of 25% a year, compared with 62% for M0 patients.

Preoperative radiological studies are nonspecific. These generally show imprecisely delimitation, non-calcified tumor masses, with a heterogeneous appearance on CT investigation, with extended cystic areas and variable contrast substance capture. In the MRI investigations can be observed on the T1 sequence in isosemnal or hypersignal secondary to the hemorrhagic foci and in the T2 and STIR sequences intense and heterogeneous hypersignal. Similar radiological aspects can be observed in Ewing's sarcomas and other small cell neoplasms. This explains why imaging investigations cannot accurately specify the histological type of the tumor. However, CT and MRI remain indispensable preoperative investigations that provide important information regarding tumor resectability and oncologic staging and oncologic staging (Ibarburen et al 1996).

The positive diagnosis of primitive neuroectodermal tumors is based on the expression of at least two neural markers and/or the presence of Homer-Wright rosettes. Immunohistochemistry, consistent with the literature, and in the case of our patient, the expression of CD-99 positive vein and ki-67 positive in 70% of the cells can be observed.

Ablative surgery, chemo- and adjuvant radiotherapy are required for the treatment of these tumors. However, the question of neoadjuvant chemotherapy and postponed surgical treatment remains open. Zimmermann at al. supports the need for neoadjuvant chemotherapy as well as for compulsory adjuvant chemotherapy and radiotherapy due to the high percentage of patients with local recurrence and post-operative distance metastases (Zimmermannet al 2001).

The role and dose of adjuvant radiotherapy remain to be discussed. The doses mentioned in the specialized literature, from 9 to 65 Gy, could not be positively correlated with the evolution of the disease (Askin et al 1979, Miser et al 1985, Seemayer et al 1975, Morrison et al 1983). However, primitive peripheral neuroectodermal tumors appear to be at least as radiosensitive as most small round cell tumors. The prognosis of patients who could not reach radical surgical resection was unfortunate, regardless of the doses of adjuvant chemotherapy and radiotherapy (Jürgens et al 1988). A study by Miser et al. contradicts this hypothesis and finds a positive correlation regarding the efficacy of adjuvant chemotherapy and radiotherapy for local control in patients with R1 resections (Miser et al 1985).

Regarding adjuvant chemotherapy, the regimens used for the treatment of Ewing sarcomas were more effective in the treatment of primitive neuroectodermal tumors than those used for the treatment of neuroblastomas. Miser et al. demonstrates superior results by administering aggressive chemotherapy, but the limits of its study are the short follow-up period of patients.

The most important prognostic factor for the evolution of the disease remains the radical surgical resection, R0 margins of the tumor.

The particularity of the case is that in the specialized literature such tumors have not been recently revealed and the most recent studies regarding this pathology is represented by a literature review that summarizes the retrospective of 89 cases. Even though most of the studies analyzed are old, this pathology is of current interest. The study is a reminder that neuroectodermal tumors continue to appear in the general population and must be identified early, treated carefully and correctly in order to achieve proper surgical results and prolong the patient's survival with good quality of life.

Conclusions

Due to their aggressive nature and low incidence, primitive peripheral neuroectodermal tumors are challenging for the clinician and require a multimodal approach, that combines surgery, chemotherapy and radiotherapy. Most patients are diagnosed at an advanced, metastatic local stage, which is associated with an unfortunate prognosis and a high mortality rate.

The peculiarity of the presented case consists in the diagnosis of a primitive peripheral neuroectodermal tumor, which has its peak of incidence, according to the specialized literature at an average age of 25 years, in a patient of 73 years. The diagnosis was formulated preoperatively through imaging investigations, with no secondary determinations observed. The positive diagnosis was confirmed postoperatively by histological and immunohistochemical investigations. The patient underwent adjuvant chemotherapy and radiotherapy and no follow-up determinations were observed at the one-year follow-up.

The difficulty of evaluating patients with primitive peripheral neuroectodermal tumors lies in the sporadicity of incidence and insufficient data for large scale studies. Research is needed in this area to develop multimodal treatment guides.

An important fact regarding this case is given by the fact that these tumors appear predominantly in young people and in the present case this type of tumor have been diagnosticated in an elderly person.

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