



Proximal type of epithelioid sarcoma presented as huge retroperitoneal mass in an old man; a case report and review of literature

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Abstract

Epithelioid sarcoma (ES) is a tumor of unknown origin as classified by the World Health Organization (WHO). It is a rare subcutaneous or deep dermal soft tissue sarcoma that was first described by Enzinger in 1970. Then, Guillou et al described a different proximal/axial deep seated type that frequently occurs in older patients. We present a case of 61-year-old male with a huge retroperitoneal mass that proved to be ES proximal type after clinical examination and investigations were done and correlated with the histopathological features including H&E stained sections and panel of immunohistochemical markers.

Introduction

Epithelioid sarcoma (ES) accounts for less than 1% of all soft tissue sarcomas with two well known types, the conventional/classic/distal type and the proximal/axial type (1). The latter is well known to develop in older age groups and with more aggressive biological behavior (2,3). ES has obscure histogenesis but exhibits clear features of epithelial differentiation, with a propensity to spread to lymph nodes. Therefore, it could be regarded as carcinoma of soft tissue. Authors suggest, it is derived from mesenchymal metaplasia, or it may represent a peculiar form of epithelioid hemangioendothelioma or malignant perineurioma (4)

This tumor shows a multinodular pattern of growth, and consists of large epithelioid carcinoma-like cells with vesicular nuclei and prominent nucleoli with characteristic granuloma like pattern of necrosis that is more apparent in the classic/distal type than in the proximal type (5). Immunohistochemically, the neoplastic cells are typically positive for vimentin, low molecular weight cytokeratin (LMWK) and epithelial membrane antigen (EMA) with 50% of the cases are CD34 positive (6). The strong co-expression of cytokeratin (CK) and vimentin is thought to be characteristic of this tumor (4).

ES can be confused with many other soft tissue sarcomas with epithelioid features, hence immunohistochemical study may be the only way to overcome this diagnostic

Key point

Epithelioid sarcoma (ES) is a rare subcutaneous or deep dermal soft tissue sarcoma. Proximal type/ES is a diagnosis of exclusion as a range of differentials needs to be kept and ruled out on the basis of the clinical profile, morphology and a wide panel of relevant immunohistochemical markers before making such diagnosis.

challenge (7).

In the present study, we present a case of proximal type ES in which a list of differential diagnosis. Clinical correlation along with the morphology of hematoxylin and eosin (H&E) stained sections and panel of immunohistochemical markers were guide to diagnosis.

Case Report

In 2015, a 61-year-old male patient presented to Ain Shams University hospital by manifestation of chronic intestinal obstruction, computerized tomography (CT) scan (on pelvis and abdomen) revealed huge retroperitoneal mass, adherent to the posterior wall of ascending colon (arise? or infiltrate it?) with heterogeneous appearance (solid and cystic areas). Clinically, the first impression that it was colonic adenocarcinoma; so carcinoembryonic antigen (CEA) and colonoscopy were done. The level of CEA was normal in the patient serum, and colo-



noscopy revealed no colonic masses or ulcers. Both liver function and kidney function were normal. The CBC of the patient was showing just normocytic normochromic anemia. Clinical examination and body scan revealed no masses in any other organ. Thus, surgeons planned to do exploration.

Exploration was done and the result was a large unresectable retroperitoneal mass adherent to the posterior wall of ascending colon and associated with mild ascites was found. Floating soft tissue fragments were found in this ascetic fluid denoting necrotic tumor fragments, the tumor was surrounding the retroperitoneal vital structures and thus, they could not resect the tumor. However, many representative incisional biopsies were performed. The surgeon noted that the mass was away from the kidney, the suprarenal gland and the pancreas but adherent to ascending colon, that clinically, the surgeon was suspecting primary retroperitoneal sarcoma as the first possibility followed by colonic gastrointestinal stromal tumors (GIST). Grossly: Incision biopsy received as multiple grayish white soft to firm tissue pieces measured collectively 6×6 cm.

Microscopic examination: All examined sections showed sheeting growth pattern of malignant epithelioid neoplasm with large polygonal cells, with abundant eosinophilic cytoplasm with some vacuolated cells. The nuclei were vesicular with prominent eosinophilic nucleoli and infrequent mitoses (Figure 1A). The nuclei were central in most tumor cells but occasional deep eosinophilic cells with nuclei pushed to one side are also noted (rhabdoid features). Areas of necrosis are seen that appeared small and palisaded by the tumor cells (pseudo granulomatous appearance) in many examined fields (Figure 1B and C). PAS stain revealed positive inclusions in some neoplastic

cells (focal) (Figure 1D).

At this level, a list of differential diagnosis was suspected. A panel of immunohistochemical markers was performed to this case including (vimentin, pancytokeratin, S100, desmin, CD117, CD31, CD34) and revealed strong diffuse staining of the neoplastic cells to vimentin (Figure 2A) and CK (Figure 2B) with patchy focal staining for S100 (Figure 2C and D). All other immunostains were totally negative including desmin, CD117, CD31 and CD34.

Discussion

ES is a unique tumor composed of cells exhibiting both mesenchymal and epithelial differentiation as evidenced by vimentin and CK expression respectively, with unknown cell of origin (8).

Proximal type of ES was first described in a study including 11 males and 7 females with most patients aged 20 to 40 years and tumor size range from 1 to 20 cm. All the studied cases were not in the retroperitoneum. Instead; pelvis, perineum, pubic region, vulva, buttock, penis, axilla and the occiput were the presenting sites (9). Then many authors reported other cases. Another study reported 20 cases ranged in age from 13 to 80 years (mean, 40 years) with 12 males and 8 females (10). Humble et al (6) reported 8 cases with an average patient age range from 43 to 76 years with the mean age was 53, the male: female ratio was 5:2, the upper extremity was the most common location presented in five cases, other sites were the lower extremity, the perineum, and the paraspinal soft tissue with one case for each. Also, a case of 47-year-old male was reported presented with a perineal soft tissue mass (11).

In this study, we present a 61-year-old male case with a huge retroperitoneal mass. All reported cases showed the

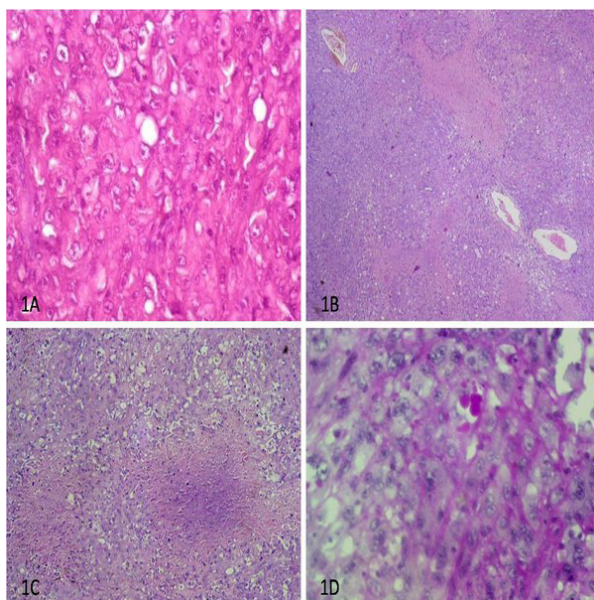


Figure 1. (A) The tumor showed the epithelioid cells with vesicular nuclei and prominent eosinophilic nucleoli, H&E, ×400; (B) The tumor showed the pseudo-granulomatous appearance of necrosis H&E, ×100; (C) higher magnification for a necrotic area palisaded by tumor cells, H&E, ×200; (D) PAS stain showed positive inclusions in few neoplastic cells, ×400.

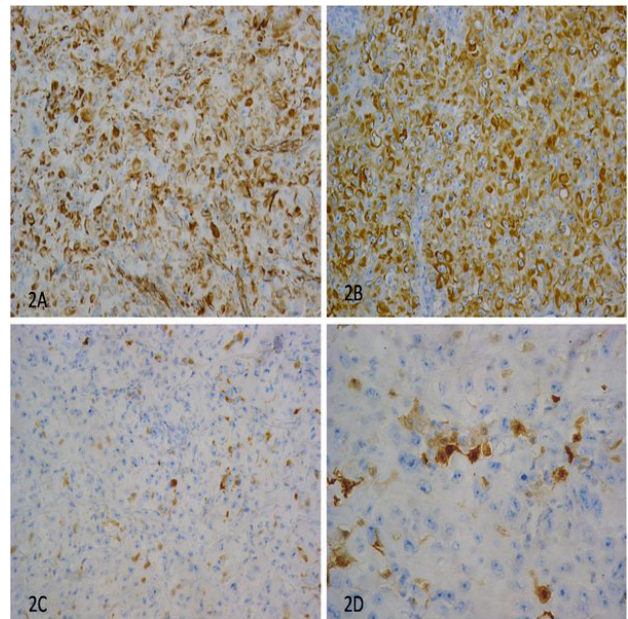


Figure 2. (A) strong cytoplasmic stain of most of the neoplastic cells to vimentin, ×200; (B) strong cytoplasmic stain of most of the neoplastic cells to cytokeratin, ×200; (C and D) Two magnifications showed the patchy stain for S100, (C) ×100, (D) ×400,

male predominance, with most of the case reports emphasizing the old presenting age for proximal type ES that reach up to 80 years (10).

Although, conventional ES typically presents as relatively small tumor less than 5 cm, the Proximal-type usually presents as larger nonspecific soft tissue mass, often with grossly apparent areas of hemorrhage and necrosis (12). This feature was in concordance with the present case in which the patient was presented by huge retroperitoneal mass. Moreover, it was reported that radiographic findings often reveal a nonspecific solid and cystic multi-lobulated lesion (13), that was in agreement with present case.

Histologically, ES is characterized by a predominantly large epithelioid cells surrounding areas of necrosis, resulting in a pattern resembling a benign necrobiotic granulomatous process (2). These atypical large epithelioid like cells would have deep eosinophilic cytoplasm and vesicular nuclei with prominent nucleoli arranged in multiple nodules with both a diffuse pattern, resembling undifferentiated carcinoma, and the granuloma-like pattern that had been already described (14).

It was found that the geographical necrosis was more evident than the necrosis with pseudo-granulomatous pattern in the proximal type of ES (15). This was explained as the deep lesions mostly are longstanding, thus fusion of the pseudo-granulomatous like necrotic areas occurred result in geographical areas of necrosis.

In the presenting case, the pseudo-granulomatous like pattern of necrosis was so evident and it was important diagnostic guide for this case. We suggest that the peripheral part of any growing tumor is retaining the characteristic growth pattern that can be seen in this neoplastic lesion and in the presenting case we got just incisional biopsies from the tumor surface (periphery).

It was reported that this tumor can show minimal pleomorphism (13). These findings were in concordance with the present case, as mild to moderate cellular pleomorphism was found. On the other hand, ES can show prominent cytological atypia with frequent occurrence of rhabdoid features (2). Also, it was mentioned that marked cytological atypia is mostly evident in the proximal type ES (15). We suggest that as the classic form usually shows bland looking epithelioid cells around the necrotic areas that can be mistaken for infectious granuloma (4), so the proximal type would also show the same morphology and with the long standing tumor; the neoplastic epithelioid cells gain more mutations with the appearance of more aggressive clones including the rhabdoid cells. Again, we receive the peripheral part of the tumor that mostly retains the characteristic morphology seen in the conventional one.

Regarding the role of special stains as PAS, Rosai (4), did not mention about PAS positive inclusions in this neoplasm that seems it is not a characteristic feature, meanwhile, they reported this finding in other neoplasms including synovial sarcoma, granular cell tumor and alveolar soft part sarcoma that were present in our differential diagnosis list. Thus, in the present case, at the beginning, ES was not the favoured diagnosis, as PAS positive inclusions

were found in some neoplastic cells, but on reviewing the reported cases, Kanai et al (16), found a case of proximal type ES that was located in the right hip-to-thigh region of a 58-year-old female. They studied the case by light microscopy including H&E stained sections, PAS stained sections, immunohistochemistry, and electron microscopy. They noted on light microscopic sections round, homogeneous, eosinophilic bodies that were PAS positive and diastase resistant. This was in concordance with the present study.

The differential diagnosis of ES is broad (8). Thus, establishing a diagnosis of ES heavily depends on the experience of the histopathologist, proper interpretation of the H&E stained sections, and comprehensive immunohistochemical analysis with the final diagnosis of ES would be made only after exclusion of the other potential neoplastic lesions. Moreover, although the proximal variant of ES is a valid entity, its diagnosis especially in old age and with classic central location as retroperitoneum should be done with high caution as the undifferentiated carcinoma would be the most suspected possibility (4). Thus, in the present case, all neoplastic lesions with epithelioid morphology were excluded before making such diagnosis depending on collaboration of clinical, radiological, histopathological parameters including panel of immunohistochemical stains. This was in agreement with Zevallos-Giampietri et al (7), who reported that since proximal-type ES can be confused with a number of other soft tissue tumors with epithelioid and/or rhabdoid features, the immunohistochemical study may be the only solving clue for these dilemma of differential diagnosis. Also, it was mentioned that immunohistochemical stains can be helpful to delineate cellular lineages (14). Thus, in the present case, the immunohistochemical panel was necessary for the final diagnosis.

The differential diagnosis of ES include many other lesions with epithelioid cells/and or rhabdoid features, such as an extra-renal rhabdoid tumor, synovial sarcoma, epithelioid angiosarcoma and melanoma (10). In addition to the previously mentioned lesions, an epithelioid GIST, an anaplastic large cell lymphoma (ALCL), and mesothelioma were also added to differential diagnosis list (11). Poisson et al (14) added a list for an epithelioid soft tissue malignancy, epithelioid type of malignant peripheral nerve sheath tumor, alveolar soft part sarcoma, epithelioid leiomyosarcoma and metastatic undifferentiated carcinoma. Also ES-like hemangioendothelioma was added to the differential diagnosis (13). We considered all these diseases in our differential diagnosis list.

In the present case, clinical, radiological and histopathological correlation was done. Thus, the immunohistochemical panel selection was largely depend on this correlation especially that in developing countries, patients had limited resources and so great value from marker choice is highly needed.

Clinical and radiological findings were important to exclude many neoplastic lesions especially carcinomas whether primary carcinoma of the retroperitoneal struc-

tures as adrenocortical carcinoma, eosinophilic variant of renal cell carcinoma, but the clinician confirmed free kidney and suprarenal glands by radiology and on exploration. Metastatic carcinoma of occult primary especially testicular or prostatic carcinomas as they can send metastasis to retroperitoneal lymph nodes (least likely as this retroperitoneal mass was very huge and body scanning revealed no more masses in any other site) were also excluded from the differential diagnosis list. Additionally, in the exclusion of mesothelioma, no peritoneal nodules and mild ascitis were present. Moreover, the main tumor bulk was retroperitoneal, hence, mesothelioma was ruled out. Immunohistochemical panel including vimentin, CK, S100, Desmin, CD117, CD31, and CD34 was selected for this case in which the differential diagnosis list includes epithelioid malignant peripheral nerve sheath tumor, malignant granular cell tumor, epithelioid leiomyosarcoma, epithelioid angiosarcoma, ES like hemangioendothelioma, synovial sarcoma, proximal type ES, alveolar soft tissue sarcoma, extra-renal rhabdoid tumor, malignant melanoma whether primary clear cell sarcoma/malignant melanoma of soft part or metastatic (excluded from the clinico-radiological metastatic work up), epithelioid GIST, and anaplastic large cell lymphoma.

After, the immunostains were done, exclusion of many retroperitoneal sarcomas was evident. Epithelioid malignant peripheral nerve sheath tumor (MPNT) should be negative for CK and strongly positive S100, unlike our case where CK was strongly positive and S100 showed focal positivity. Malignant granular cell tumor shows strong PAS stain, negative CK and positive desmin immunohistochemical expression, while this case was focally positive for PAS stain, positive for CK and negative for desmin. Although, epithelioid leiomyosarcoma can show positive vimentin and CK, it was expected to show positive desmin stain. Negative immunohistochemical expression for desmin in our case excluded the possibility for both epithelioid leiomyosarcoma and solid alveolar soft part sarcoma, excluded also from diagnosis as it is characterized by strong PAS positive inclusions and development in younger age group. Epithelioid angiosarcoma was not favoured on H&E stained sections as no prominent vascularity with small or large freely anastomosing vessels lined by atypical endothelial cells were noted, moreover the tumor was negative for both CD31 and CD34 which are regularly expressed in angiosarcoma. ES like hemangioendothelioma was one of the most important potential diagnostic neoplastic lesion, but negative CD31 immunostain made it unfavoured. Although many authors consider extra-renal rhabdoid tumor in the differential diagnosis, the occasional rhabdoid features and the old patient age make this diagnosis unfavourable (4).

Malignant melanoma whether primary clear cell sarcoma (malignant melanoma of soft part) or metastatic secondary to primary skin or other organ lesions was excluded as it didn't show co-expression of vimentin and CK. Moreover, S100 stain was expected to be diffuse as well as scanning of the patient body revealed no more lesions elsewhere (15).

Although colonic GIST was suspected clinically, contact with surgeons revealed that primary retroperitoneal sarcoma is the most favoured for this patient and the tumor was negative to CD117 and CD34 thus, colonic GIST became unfavoured. Anaplastic large cell lymphoma was excluded as it did not express vimentin or CK in addition to the morphology by H&E which was not favouring anaplastic large cell lymphoma in absence of horseshoe shaped or multilobed pleomorphic nuclei (4).

The remaining tumors in the differential diagnosis list are synovial sarcoma and proximal type ES. Although, CD34 is considered important differentiating marker as it is negative in synovial sarcoma and positive in 50% of ES; in the presenting case, negative stain for this marker was found thus synovial sarcoma may be considered but ES could not be excluded. Revision of H&E stained sections, favoured ES as pseudo-granulomatous like necrosis with the large deep eosinophilic neoplastic cells are seen in this neoplasm. Moreover, according to the literature, the neoplasm can be presented in old age as our presenting case.

It was reported that ESs regularly express vimentin, CKs, EMA, and about half of the cases are CD34 positive. Other antigens including S100 protein, smooth muscle actin and desmin are usually negative (2,13,17). Moreover, strong co-expression of vimentin and CK is thought to be characteristic for this neoplasm (4). In the present study, strong co-expression of vimentin and CK was noted that raise the possibility of this tumor especially in the presence of clinical suspicion of primary soft tissue sarcoma and absence of any primary carcinoma elsewhere.

Although, S100 is considered a negative marker for ES (2,4,13,17), Hasegawa et al (10) reported that out of their studied 20 cases, 12 cases (60%) were focally positive for S-100 protein that was in agreement with the present case as patchy focal stain to S100 was also found.

Total negative stain for other markers including CD31, CD34, CD117, and desmin was found. In concordance with the present study, Hasegawa et al (10) reported that all their studied 20 cases (100%) were negative for Muscle-specific actin, myogenin, and CD31.

Accordingly, Rekhi et al (11) reported a case of 47-year-old male presented with a perineal soft tissue mass that proved to be ES after the clinico-radiologic metastatic work-up, revealed no definite mass in the solid organs. In their case, CEA was done and found to be normal as our presented case. Similar to our case, a large panel of immunohistochemical markers was done that included vimentin, CK, desmin, CD34, smooth muscle actin, S100, CD117 (C-kit), and CD31, and in which positivity to vimentin, CK and CD34 and the negativity for other mentioned markers helped them to reach a definite final diagnosis. Accordingly, the case was signed out as ES proximal variant.

Conclusion

Proximal type/ ES is rare and is a diagnosis of exclusion as a range of differentials needs to be kept and ruled out on the basis of the clinical profile, morphology and a wide panel of relevant IHC markers before making such diagnosis.

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Authors' contribution

Both authors contributed to the design of the research. SAS and MMS shared in analysis and interpretation of data. Both authors drafted the first version. SAS and MMS edited the first draft. Both authors reviewed and commented on final draft.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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