Perineal mass in a 50-year-old man

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CLINICAL HISTORY

A man in his fifties presented with a lump in his left anal/perineal region, which was clinically thought to be a lipoma and was excised. No preoperative imaging was available. Review the high-quality, interactive digital Aperio slide at http://virtualacp.com/JCPCases/jclinpath-2019-206337/ and consider your diagnosis.

WHAT IS YOUR DIAGNOSIS?

A. Epithelioid angiosarcoma (EAS).
B. Epithelioid malignant peripheral nerve sheath tumour (eMPNST).
C. Malignant rhabdoid tumour (MRT).
D. Melanoma.
E. Proximal epithelioid sarcoma (ES).
F. Pseudomyogenic haemangioendothelioma (PH).

The correct answer is after the Discussion.

DISCUSSION

The diagnosis in this case is proximal ES. This was based on the following morphological features and immunohistochemistry. The sections show a cellular tumour composed of large polygonal cells with vesicular nuclei with prominent nucleoli and abundant eosinophilic granular cytoplasm (figure 1A). There are 8 mitoses per 10 high-power fields and focal necrosis. The tumour grows in sheets to form large nodules with a mild intratumoural lymphoid population and infiltrates into the surrounding fibroadipose tissue. The morphology and the immunohistochemistry findings are in keeping with proximal-variant epithelioid sarcoma (PES). The tumour shows strong and diffuse expression of epithelial membrane antigen (EMA) and CD34, with patchy expression of AE1/AE3 (figure 1B,C). There is also loss of nuclear expression of INI1 (figure 1D). There is no expression of MNF116, CAM5.2, S100 protein, CD30, CD31, FLI1, ERG, SOX10, HMB45, MelanA, desmin, smooth muscle actin (SMA), myogenin, CD45, PLAP or prostate-specific antigen.

Like PES, eMPNST can show a nodular growth pattern with large rounded cells, but often shows spindle cell areas.[1] eMPNST more frequently occurs on extremities and may involve both superficial and deep compartments.[1] eMPNST can be associated with nerves or neurofibroma, unlike PES.[1 2] INI1 loss is also seen, although only in approximately 50% of eMPNST,[1] and unlike EAs, 80% are positive for S100 protein, and eMPNST typically lacks cytokeratin expression.[1 2] EAS usually occurs in older patients and more frequently involves the viscera or deep soft tissues. The focal dyscohesion of cells in PES may give a pseudovascular appearance, but true vasoformation is absent.[1] PES and EAS show an overlap of immunohistochemical findings. Both are positive for CD34, and EAS is often strongly positive for pancytokeratins and can be positive for EMA, while up to 38% of epithelioid sarcomas are positive for ERG.[3 4] EAS is also typically strongly positive for CD31, factor 8-related antigen and FLI1, unlike EA, and only rarely shows nuclear INI1 loss.[1 3 4] MRTs are usually seen in younger patients than ES, with most presenting under the age of 3 years.[1] The growth pattern is less nodular, with infiltrative sheets of tumour.[1] Immunohistochemically, all MRTs and 81%–90% of ES show INI1 loss, and while both express cytokeratins, this is typically limited to CK8 and CK18 with a dot-like staining pattern in MRT.[1 5] MRT also lacks CD34 expression, which is characteristic in ES.[1] While both tumours show nuclear INI1 loss by immunohistochemistry, mutation of the *SMARCB1/INI1* gene is much more frequent in MRT. Exclusion of melanoma should be straightforward; the patient may have a previous history of this neoplasm, and the immunoprofile differs markedly from PES, with typically strong expression of SOX10, S100 protein and melanocytic markers such as HMB45 and Melan-A. PH (also known as ES-like haemangioendothelioma) can occur in a similar demographic to ES. PHs typically arise in the limbs and can involve any tissue plane.[1] These grow as sheets or fascicles of spindle to ovoid cells, with an infiltrative pattern. The cells have vesicular nuclei, prominent nucleoli and eosinophilic cytoplasm, and some have an appearance resembling rhabdomyoblasts.[1 6] PHs are characteristically positive for ERG, FLI1 and AE1/AE3, but, unlike ES, lack MNF116 and CD34 expression, and EMA is absent or weak.[1 6] In addition, nuclear INI1 expression is retained, in contrast to the loss seen in the majority of ESs.[6]

PES is a rare tumour which is usually seen in adults (13–80 years, median 40 years) with a slight predominance in men.[7] Almost all present with a palpable mass and less frequently with pain.[7 8] It is often deeply situated, involving proximal/axial sites, and more rarely peripherally and/or in the subcutis.[8 9] Classical ES occurs more frequently at peripheral sites, in particular, the superficial distal upper extremities. While it shares an immunoprofile with PES, it is characterised by granuloma-like lesions with central necrosis and typically smaller, more uniform epithelioid cells that lack the more notable anaplasia of those of PES.[1] The proximal variant of ES has a more aggressive clinical behaviour than the classical variant and carries a poor prognosis, typically manifesting as larger tumours with

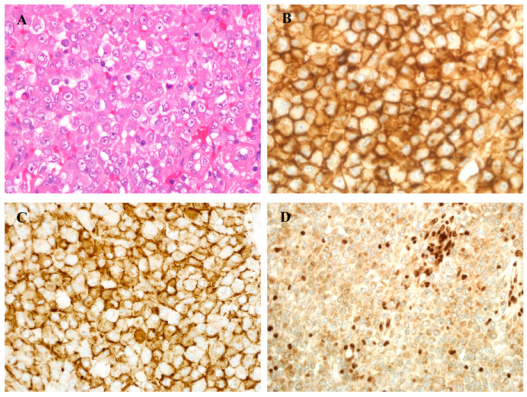

Figure 1 Scanned virtual slide (proximal-type ES). Proximal-type ES. (A) The tumour is composed of sheets and nests of relatively large and monomorphic epithelioid cells with vesicular nuclei and prominent nucleoli. (B,C) There is diffuse and strong expression of CD34 (B) and epithelial membrane antigen (C). (D) immunohistochemistry for INI1 shows widespread loss of this marker in tumour nuclei. ES, epithelioid sarcoma.

early metastases.[7 8] In one series, recurrence occurred in 65% of patients after a median of 10 months, frequently repeatedly.[7] Seventy-five per cent of patients developed metastatic disease following a median of 2 years and 4 months (most frequently to lymph nodes, lung, bone and skin).[7] Macroscopically, tumours are multinodular and ill-defined, pale grey to white masses, occasionally with haemorrhagic and/or necrotic areas.[7 8] Microscopically, the findings are of infiltrative nodules comprising variable proportions of rhabdoid cells with intracytoplasmic inclusions, and of large round to polygonal cells with abundant amphophilic cytoplasm and either vesicular nuclei with prominent nucleoli, or hyperchromatic nuclei with indistinct or small nucleoli.[7 8] Occasionally, there are smaller numbers of admixed spindle cells.[7–9] The tumour may show areas of dyscohesion, giving a pseudovascular appearance.[7 8] The tumour is focally to diffusely positive for cytokeratins, usually positive for EMA (85%–94%), and may be focally or diffusely positive for CD34 (45%–50%).[7 8 10] There can be occasional expression of CD99 (25%), HMB45 (23%), S100 protein (0%–30%), SMA (5%–33%), desmin (10%–63%, mostly in rhabdoid cells), CD56 (5%), synaptophysin (20%), neuron-specific enolase (40%) and neurofilament (8%–25%).[7 8] ES is negative for CD31, and most show loss of nuclear INI1 expression.[5 8 11] The Ki67 proliferation index ranges from 5% to 90%, with a median of 50%.[7] Inactivation of the *SMARCB1/INI1* gene has been found in some cases of proximal ES; however, the genetic abnormalities involved in this are heterogeneous.[12] There is limited evidence regarding the optimal treatment of proximal-type ES. Doxorubicin–ifosfamide has been reported to achieve stable disease in some cases, and numerous potential targets for therapy have been identified, so accurate diagnosis of this neoplasm is important for future targeted treatment strategies.[13]

Take home messages

- Proximal-type epithelioid sarcoma (ES) occurs in an older patient population than classical-type ES.
- It frequently arises in the deep proximal/axial sites.
- The morphology is of infiltrative nodules of variable amounts of rhabdoid and polygonal cells with abundant amphophilic cytoplasm, occasionally with smaller numbers of of spindle cells.
- Most proximal-variant epithelioid sarcomas are positive for cytokeratins and epithelial membrane antigen, with loss of nuclear INI1 expression, and approximately half express CD34.
- The morphology and immunoprofile of proximal-type ES can overlap with a variety of epithelioid neoplasms, including undifferentiated carcinoma, epithelioid angiosarcoma and other epithelioid soft tissue neoplasms.
- Accurate diagnosis is essential because of the characteristic genetics (inactivation of the *SMARCB1/INI1* gene) and the potential for targeted therapies in the future.

ANSWER

E. Proximal epithelioid sarcoma (ES)

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