Peripheral primitive neuroectodermal tumour – a rare cause of a popliteal fossa mass: A case report and review of the literature

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A literature review of peripheral primitive neuroectodermal tumours illustrated with an index case report describing an 80-year-old woman who presented with a mass in the left popliteal fossa is presented. An excision biopsy was performed, revealing a possible peripheral primitive neuroectodermal tumour as the primary pathology. Normally confined to the chest wall and axial soft tissues of children and young adults, reports of this tumour existing in other areas and in the elderly population are scarce.

Key Words: *Ewing sarcoma; PNET; Primitive neuroectodermal tumour; Small round cell tumour*

CASE PRESENTATION

An active 80-year-old woman presented to her local doctor with a lesion in her left popliteal fossa. The patient had no history of trauma to the area, no pain from the lesion and, aside from some discomfort due to the lesion's location and tendency to bleed, experienced no other local or systemic symptoms. First noticed by the patient in mid December as a hard blood blister, the lesion grew rapidly and, when it was excised in early February, it measured 25 mm × 23 mm. Initial histopathology described it as a neoplastic infiltrate involving dermis and subcutis of uncertain histogenesis. A computed tomography scan of her chest, abdomen and pelvis was conducted in mid February, which showed no evidence of metastatic disease. Due to the uncertainty of the diagnosis, the patient was referred to a tertiary centre for expert opinion. In early March, following specialized staining tests, a supplementary pathology report was issued favouring the lesion as a malignant small round cell tumour consistent with primitive neuroectodermal tumour (PNET). Clinical examination by the radiation oncology team in March suggested local recurrence that was confirmed with a positron emission tomography scan, focal lymphadenopathy and, additionally, two suspicious lung lesions. Re-excised in April by the plastics and reconstructive surgical team, the visible lesion had regrown to approximately 70 mm in length (Figure 1).

Intraoperatively, the exophytic mass was found to have a large subcutaneous compartment, tracking between the muscles both proximally and distally. Due to the depth of its involvement with the neurovascular bundles, clear margins were unable to be obtained. A repeat computed tomography scan performed postoperatively showed 25 new soft tissue nodules throughout the lungs with bulky hilar lymphadenopathy. The two lesions observed on the positron emission tomography scan one month earlier had grown dramatically, one growing from 9 mm to 25 mm. No lesions were noted elsewhere.

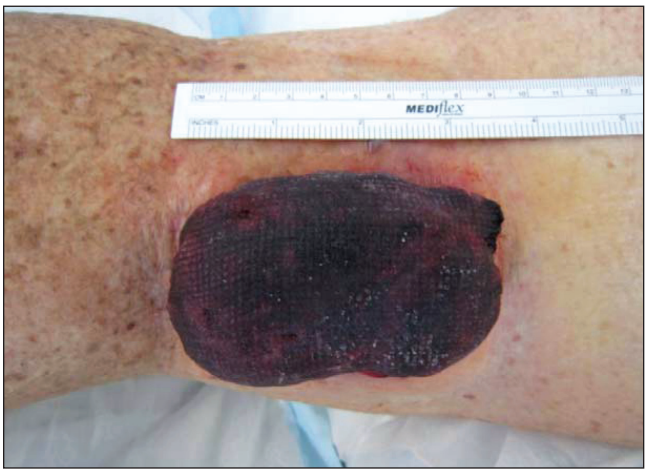

Figure 1) *Popliteal mass*

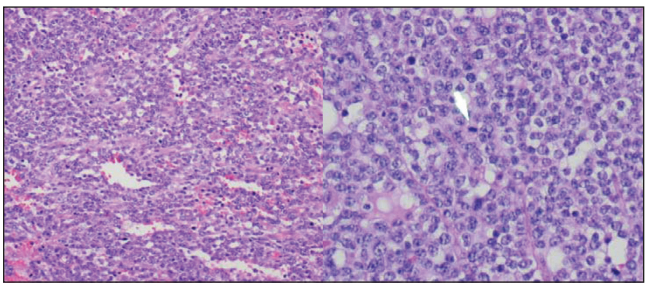

Figure 2) *Hematoxylin and eosin stain of the popliteal tumour. Original magnification ×66 (left); ×132 (right)*

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TABLE 1
Differential diagnosis of popliteal fossa masses

Tissue type	Examples
Skin and subcutaneous tissue	Sebaceous cyst, carbuncle, lipomas, abscess, hemangiomas, skin malignancies, sarcomas, cellulitis
Muscle	Contusions of gastrocnemius or semimembranosus
Bursae	Synovial cysts (Baker), meniscal cysts, popliteal cystic tumours
Vascular	Varicocele, thrombophlebitis, arteriovenous malformations/fistulas, aneurysms, vascular tumours, deep vein thrombosis
Lymphatics	Enlarged popliteal nodes (secondary to tuberculosus adenopathy, distal infection or metastatic malignancy), lymphangioma
Nerves	Nerve sheath tumours (eg neurilemoma), peripheral nerve tumours (eg, perineuroma, PNET), neurofibroma, ganglion
Bone, periosteum and cartilage	Exostosis arising from epiphyseal cartilage of femur in children, medullary giant cell tumours, fibrosarcomas of the periosteum, osteomyelitis, fractures, chondroma

*Data adapted from **references 1 and 2**. PNET Primitive neuroectodermal tumour*

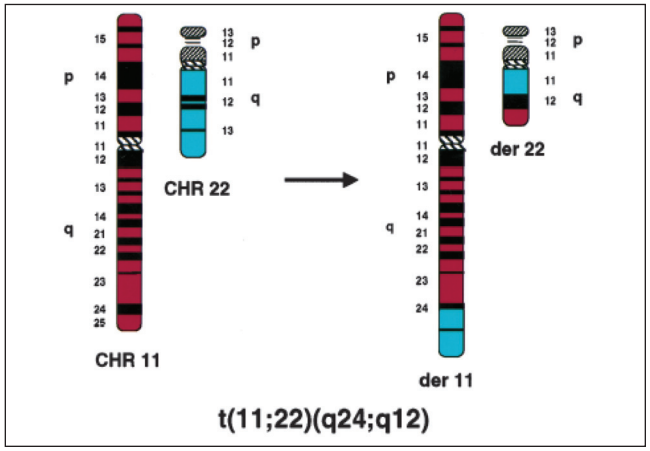

Figure 3) *Schematic diagram of t(11;22)(q24;q12), observed in up to 85% of Ewing sarcoma/peripheral primitive neuroectodermal tumour. Adapted from reference 16*

Microscopic findings showed a poorly differentiated tumour composed of small round cells with uniform nuclear features, occasional prominent nucleoli and indistinct cell borders (Figure 2). Occasional conspicuous Homer Wright-like rosettes were identified. The tumour was noted to have invaded fat, muscle and vascular tissue. Immunohistochemistry was positive for CD99, vimentin, BCL2 and CD56. Fluorescence in situ hybridization (FISH) studies were negative for the synovial sarcoma rearrangement (18q11.2) and Ewing sarcoma (ES) rearrangement (22q12). Due to classical morphology and immunohistochemistry staining, PNET was favoured while other differential diagnoses, such as Merkel cell tumour, lymphoma, rhabdomyocarcoma, synovial sarcoma, melanoma and carcinoma, were excluded. Because typical translocation could not be found in the FISH study, it was believed this may reflect a subgroup of peripheral PNETs (pPNETs), which lack this genetic change. The patient was referred for local radiation oncology and systemic chemotherapy.

DISCUSSION

Differential diagnosis of popliteal fossa masses

In adult patients, the most common cause of a popliteal mass is a Baker cyst. The differential diagnosis, however, is quite extensive. Classification according tissue type can assist with identifying the pathology (Table 1).

pPNETs

pPNETs are an extremely rare cause of a popliteal mass. Believed to originate from migrating embryonic cells of the neural crest (3), pPNETs are most commonly found in the chest wall and axial soft tissues (4,5), although they have been diagnosed in other areas including bone, extra-axial soft tissue and visceral tissues (6-11). Belonging to a family of 'small round-cell tumours', they are most frequently observed in children and young adults, but can occur at any age (12,13). Due to their aggressive nature, distant micrometastasis must always be assumed to be present and, hence, all patients should receive adjuvant chemotherapy for systemic control (13,14).

pPNETs are commonly classed with ES and Askin's tumour (pPNETs limited to the thoracopulmonary region) as members of the Ewing family of tumours (8,12,13,15-17). They have almost identical pathological, immunohistochemical and genetic features, with the main distinct difference being that tumours demonstrating neural differentiation are labelled pPNET while those that are undifferentiated are diagnosed as ES (3,12,15,18,19). Due to this subtle distinction between ES and pPNET, diagnosis can only be made with immunohistochemical, electron microscopy and molecular biological studies (19). The phenotypic expression distinction has, however, no clinical significance (15).

Epidemiologically, pPNET has a peak incidence in the second decade of life, with 80% of presentations <20 years of age (15,16). ES and pPNET account for 6% to 10% of primary malignant bone tumours following osteosarcoma as the second most common group of bone sarcomas in children (15,20). It is slightly more prevalent in males and more common in whites and Hispanic populations, while rare in African and Asian populations; the reasons for this are currently unknown (16,21).

Due to its insidious onset, patients often present with a large tumour, and as many as 20% to 25% already have detectable distant metastatic disease most commonly to the lung, bone and/or bone marrow (13,22-24). Nearly all, however, have micrometastases as indicated by a 10% cure rate with local therapy alone (16). In addition to localized symptoms (pain, swelling, bleeding), systemic findings can occasionally occur including fever, elevated erythrocyte sedimentation rate, anemia and leukocytosis (15).

Radiologically, pPNETs often have a large soft tissue component (>5 cm on average) and show moderate enhancement with intravenous contrast, combined with nonenhancing necrotic areas (13). These necrotic areas tend to displace rather than encase adjacent organs. If they do involve adjacent bone, however, they tend to exhibit lytic/erosive change (13).

Macroscopically, pPNETs are usually soft, tan-white in colour, and frequently contain areas of hemorrhage and necrosis with calcification also noted occasionally (13,15). Microscopically, they typically consist of sheets of small monomorphic round dark cells with small hyperchromatic inconspicuous nuclei and scant cytoplasm (25). Extensive necrosis is usually present (16). A common finding in pPNET is the presence of Homer Wright rosettes (tumour cells arranged in a circle about a central fibrillary space), which is indicative of neural differentiation (7,15,26).

Because pPNET shows neuroepithelial differentiation, immunohistochemistry can be used to test for neurospecific proteins including NSE, Leu-7, enolase, synaptophysin, S-100 protein, PGP 9.5, secretogranin II, vimentin and keratin (19,27). Additionally, electron microscopy can also be used to reveal features of neural differentiation (eg, neurosecretory granules, neurofilaments and neurotubules) (28).

Eighty-five percent of tumours diagnosed as either ES or pPNET have the translocation t(11;22)(q24;q12) (15,16) (Figure 3). This translocation results in the division of two genes known as Friend

TABLE 2
Five-year local recurrence rates

Author (reference)	Patients, n	Five-year survival rate, %		
		Overall	If metastasized at diagnosis	If localized disease only at diagnosis
Baldini et al (18)	37	37	0 (n=11)	49 (n=24)
Kolb et al (22)	68		17.8 (four-year survival) (n=24)	89 (four-year survival) (n=44)
Smorenburg et al (25)	27	58	60 (n=10)	52 (n=17)
Martin and Brennan (35)	59	60	33	60
Fizazi et al (21)	182	41	9 (n=53)	54 (n=129)

leukemia virus integration 1 (*FLI-1*) gene and ES (*EWS*) gene. The *FLI-1* gene on 11q24 is a member of a large family of DNA-binding transcription factors that are implicated in the control of cellular proliferation, development and tumorigenesis (14,29). The *EWS* gene on 22q12 is believed to be involved in messenger RNA transcription (30). These two genes fuse to form a functional *EWS-FLI-1* gene, which results in abnormal cell proliferation and survival (16). This gene rearrangement is detected with FISH studies and is pathognomonic of ES/PNET (19). The remaining 15% have variants including 22q12,21q2 (10%), 7p22, 17q12 and 2q36 (<1%) (19).

Another highly specific test performed to identify a pPNET is immunohistochemical staining of an antigen for the *MIC2* gene. The product of the *MIC2* gene – CD99 – is a cell surface glycoprotein involved in cell adhesion. It is highly sensitive for pPNET; however, it has been known to occur in other tumours, such as 30% of carcinoid tumours, thus lacks specificity (26,31-33).

Treatment for pPNET consists primarily of systemic intensive multi-agent chemotherapy with surgery and/or radiotherapy for local control, inoperable tumours or lesions unresponsive to chemotherapy (16,22), although the relative efficacies of these local treatments remain controversial (18). Multi-agent chemotherapy is recommended due to the tumour's strong propensity for metastasis (18). In one study, chemotherapy has been shown to improve five-year survival from 5% to 15% to 75%, with up to 50% having long-term cures (15). In 2003, Shamberger et al (34) suggested that the preferred treatment sequence is after initial biopsy for adjuvant chemotherapy with delayed resection after four courses of treatment. This is believed to avoid the need for radiotherapy (and associated complications).

Although study numbers are relatively small, five-year survival rates are approximately 40% to 60%, with patients with metastatic disease at diagnosis having a much poorer outcome well below 30% five-year survival (18,25,35) (Table 2). Consistently adverse prognostic factors include larger tumour size (>5 cm to 8 cm), metastasis at time of diagnosis and bone metastasis (9,18,25,36-38).

Several studies have reported a poorer prognosis with older patients (18,39); however, this finding is not consistent across all studies (40). A study by Verill et al (37) involving 59 patients showed adults had a similar prognosis, with a 38% five-year survival rate (52% if localized). A reason proposed by Baldini et al (18) for more favourable outcomes in younger patients is that they have more bone marrow reserve to tolerate the long chemotherapy regimens that have been used. Five-year local recurrence rates are approximately 15% (18,35,41).

The incidence of pPNET is likely to be under-reported in the literature. Recent cytogenetic and immunohistochemical advances have enabled these tumours to be distinguished from other small, poorly differentiated round cell tumours such as neuroblastoma, rhabdomyosarcoma and lymphoma (42). Research investigating targeted molecular therapies is underway (43).

CONCLUSION

The present case demonstrates a rare pathology not only for this age group but also for a popliteal fossa mass. It is always important to consider the rare and serious causes when diagnosing a lesion.

CONSENT: Informed, written consent was not obtained from the patient for publication of this case report and any accompanying images but there are no patient identifiable images used in this article.

DISCLOSURES: The authors have no financial disclosures or conflicts of interest to declare.

AUTHORS' CONTRIBUTIONS: CD and AC performed the literature review and drafted the manuscript. TT performed the histological analysis and critically reviewed the manuscript. DS, SS and VH operated on and supervised the care of the patient and critically drafted the manuscript. All authors read and approved the final manuscript.

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