Ewing sarcoma (ES)/primitive neuroectodermal tumor (PNET) is a malignant small round blue cell neoplasm of presumed neuroectodermal origin that affects bones and soft tissue in children and young adults. Nearly 80% of the patients are younger than 20 years. The tumor cells characteristically express CD99 (MIC2 antigen), a glycoprotein localized on cell membrane. The defining feature of ES/PNET is a characteristic translocation t(11;22)(q24;q12) involving the EWSR1 gene on chromosome 22 and the FLI1 gene on chromosome 11.

ES/PNET in parenchymal organs are rare. A review of the English literature revealed 12 additional cases, and confirmed that ES/PNET of the adrenal gland is a rare, aggressive and lethal tumor. The patients including the present case ranged in age from 4 to 57 years (median age 22), most were children (5/13) or young adults (6/13), and only two patients were older than 30 years. There was no particular predilection for gender or laterality. The tumors were large (range 5 to 17 cm), solid and cystic, hemorrhagic and necrotic. Interestingly, four of the tumors including the present case showed involvement of the inferior vena cava by direct extension of tumor thrombus that in one case reached the right atrium, a feature that appears to be unique to adrenal ES/PNET. Follow-up in 12 cases shows that the tumors were aggressive and lethal leading to death in seven and progression in three patients within two years of diagnosis. Eight patients had metastasis at presentation or developed it during follow-up. Only two patients including the present case achieved complete remission after surgery, chemotherapy and radiotherapy.

ES/PNET of the adrenal gland can be easily misdiagnosed as neuroblastoma, an embryonic neoplasm of the sympathetic nervous system. Both tumors share the morphology of small round blue cell tumors. However, the biology, treatment and prognosis of these two tumors are entirely different. More than 90% of the neuroblastomas affect infants and toddlers, whereas the youngest patient with ES/PNET of the adrenal gland was 4 years old. Spontaneous regression may be seen in 25% of neuroblastomas and cure rates remain very high even in disseminated disease (stage IV), unlike ES/PNET. Thus, it is critical to differentiate the adrenal ES/PNET from neuroblastoma. Tumor cells in neuroblastoma may show neural and neuronal differentiation including ganglion cells, rosettes, and neuropil. Some ES/PNET may also show Homer-Wright rosettes or rosette-like structures. Several immunohistochemical markers, e.g. neuron-specific enolase, chromogranin-A, synaptophysin, and neurofilament may be expressed in both tumors. However, ES/PNET show high levels of the cell surface glycoprotein CD99 (MIC2 gene product), a highly sensitive though not specific immunohistochemical marker. Greater than 95% of ES/PNET are positive for CD99, whereas neuroblastomas are negative. The final confirmation is provided by the demonstration of the characteristic translocation t(11;22)(q24;q12) involving the EWSR1 gene that defines ES/PNET, using various techniques like cytogenetics, RT-PCR for the fusion transcript and in-situ hybridization. In the current case, we used a dual color break-apart probe to detect EWSR1 gene rearrangement by fluorescence in-situ hybridization. While less specific than other techniques, in combination with the characteristic morphology and immunohistochemistry, this supports the diagnosis.
Metastatic ES/PNET must be considered before concluding an adrenal origin. The present case underwent extensive imaging work up that failed to reveal any other site of tumor. Other small round blue cells included in the differential diagnosis are alveolar rhabdomyosarcoma, lymphoma, poorly differentiated neuroendocrine carcinoma, and melanoma. Employing a panel of myogenic, lymphocytic, epithelial, and melanocytic differentiation markers can sufficiently rule them out.

Direct extension of tumor thrombus into the inferior vena cava is characteristic of adrenal cortical carcinoma, a differential diagnostic consideration in children and young adults with large adrenal neoplasms. This was also seen in nearly one third (4/13) of the reported cases of adrenal ES/PNET. Morphologically, adrenal cortical carcinoma is an epithelial tumor comprised of large epithelioid cells with moderate to abundant cytoplasm that are typically positive for inhibin, melan-A, and calretinin, unlike ES/PNET.

In conclusion, adrenal ES/PNET is a rare tumor with a poor prognosis. It should be considered in the differential diagnosis of small round blue cell tumors of the adrenal gland. Immunohistochemical and molecular tests are necessary to make the definitive diagnosis.

References