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Case Report

Striking Multinucleated Giant Cells in Fine Needle Aspiration Specimens and Their Values in Diagnosis of Soft Tissue Tumors

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Abstract

The presence of multinucleated giant cells in fine needle aspiration (FNA) specimens of neuroblastic tumors is not uncommon, but they are often not well-illustrated in the literature. The authors present a case of a 3-year-old boy with a large abdominal mass that was found to have striking multinucleated giant cells on FNA. The FNA specimen showed a cellular smear with a predominance of small, round cells with scant cytoplasm and hyperchromatic nuclei. There were also numerous multinucleated giant cells, some of which had up to 10 to 20 nuclei. The giant cells contained abundant cytoplasm and prominent nucleoli. The patient was subsequently diagnosed with ganglioneuroblastoma. The authors discuss the differential diagnosis of multinucleated giant cells in FNA specimens and argue that these cells can be a helpful diagnostic clue in the diagnosis of ganglioneuroblastoma. The importance of recognizing multinucleated giant cells in FNA specimens of other soft tissue tumors is also discussed.

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Introduction

While it is true that multinucleated giant cells are not entirely unmentioned in the literature on fine-needle aspiration (FNA), specimens of neuroblastic tumors, their presence, and diagnostic significance often remain shrouded in relative obscurity. Despite being encountered with somewhat surprising regularity in clinical practice, these fascinating cellular formations have not received the level of detailed illustration and emphasis they deserve in existing medical texts and research articles. This lack of comprehensive exploration creates a knowledge gap for pathologists and cytologists facing these intriguing findings in their diagnostic endeavors. This manuscript was prepared according to the CARE guidelines, and the associated checklist was completed.

Case presentation

A three-year-old male presented with a large abdominal mass, with cytology preparations showing impressive multinucleated giant cells. The patient initially had a history of abdominal pain, and ultrasound and CT scans showed a large retroperitoneal mass; a biopsy of the mass was evaluated by fine needle aspiration. The lesion at the intraoperative consultation was considered "adequate". Cores were saved in RPMI medium and submitted for flow cytometry/ancillary studies. Figures 1a, b, and 2 provide representative images. A fascinating observation is the conspicuous spread of multinucleated giant cells. What is your diagnostic impression?

Morphology Analysis. 1) Cytology per FNA. Overall, the medical staff experienced significant difficulty in properly interpreting the findings, partially due to incomplete clinical and radiological information. Among the options, the possibility of a giant cell tumor was considered, as well as hematopoietic tumors and both Hodgkin's and non-Hodgkin's lymphoma. Later, their attention turned seriously to the possibility of a neuroblastic tumor, particularly ganglioneuroblastoma and ganglioneuroma, and a tentative diagnosis of a neuroblastic tumor was made. 2) Histology. The diagnosis was quickly confirmed after examination of the surgical specimen. The tumor was indeed a neuroblastic tumor, with overall unfavorable histology and two distinct components The first component was Schwannian stroma-rich, showing intermixed immature cells (maturing neuroblasts to immature ganglion cells) and a low mitosis karyorrhexis index (MKI), interpreted as favorable histology; the second one was Schwannian stroma-poor, with poorly differentiated neuroblastoma and at least intermediate MKI, deemed as unfavorable histology. Taken together, the likely subtyping is a composite ganglioneuroblastoma, or in terms of INPC ganglioneuroblastoma, nodular (UH/FH). (INPC, International Neuroblastoma Pathology Classification; UH, unfavorable histology; FH, favorable histology). Multinucleated giant cells

Keywords: Multinucleated giant cells; Fine-needle aspiration (FNA); Neuroblastic tumor; Ganglioneuroblastoma; Soft tissue tumors.

Abbreviations: FH, favorable histology; FNA, fine needle aspiration; INPC, international neuroblastoma classification; JXG, juvenile xanthogranuloma; MKI, mitosis karyorrhexis index; NSE, neuron-specific enolase; UH, unfavorable histology.

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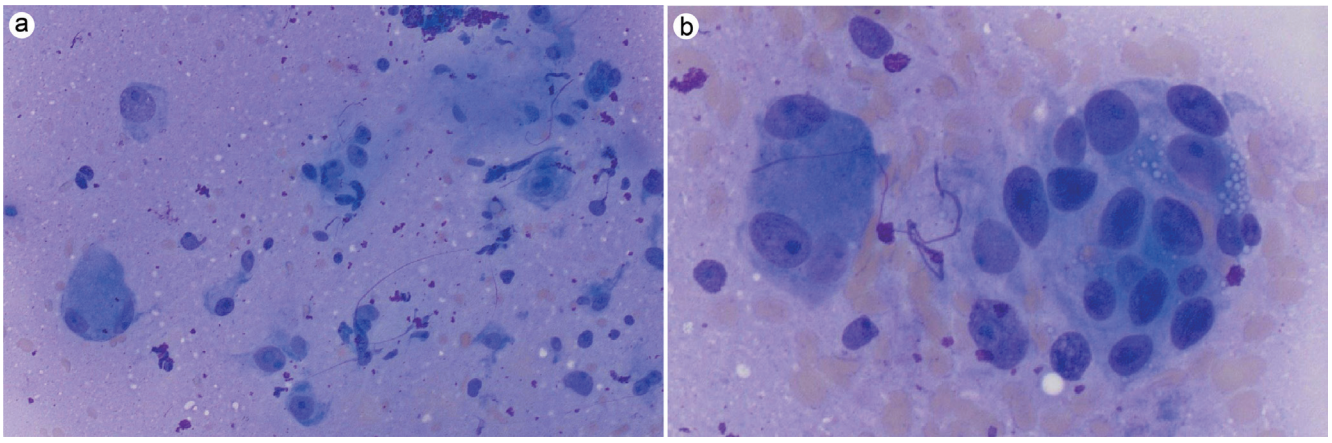

Fig. 1. Cytologic features of multinucleated giant cells in a retroperitoneal mass. (a) Touch prep Diff-Quick staining shows numerous multinucleated giant cells, some of which have between 10 and 20 nuclei. (b) These nuclei typically have smooth nuclear membranes and prominent nucleoli. Cytoplasmic vacuoles occasionally are also observed, projecting a bubbly appearance. The cytoplasm tends to be ample with a bluish hue. Magnifications: a: 200×; b: 400×.

were noted—they were neuroblasts and immature ganglion cells in various stages of maturation. Also noted were foci of microcalcification and striking multinucleation in the stroma-rich component correlated well in the cytology specimen (Figs. 3–5). Immunohistochemistry staining results, including NSE (neuron-specific enolase) and synaptophysin, were confirmatory.

The study was performed following the ethical standards of the institutions to which we are affiliated and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report.

Discussion

Cytopathology of neuroblastic tumors: The common references including standard textbooks, literature, and internet searches made scant mention of the cytology spectrum of neuroblastic tumors. The general knowledge of the subject is outlined as follows: 1) Undifferentiated neuroblastomas are, in theory, malignant small round cells indistinguishable from other round-cell tumors of children; 2) In poorly differentiated to differentiating cases, Homer-Wright rosettes and collections of neuropils can be identified; 3) In ganglioneuroblastoma cases, a biphasic pattern is expected, with one component identical to neuroblastomas and the other consisting of ganglion cells, nerve tissue fragments, and fibrillar material (Schwannian stroma). Of special note, the classic ganglion morphology features eccentric nuclei, amphophilic granular cytoplasm, and prominent nucleoli.

Although briefly touched upon, no literature sufficiently detailed the spectrum of neuroblasts and ganglion cells or stressed the phenomenon of maturing neuroblasts or immature ganglion cells being multinucleated. Publications such as DeMay, Koss, and Melamed mention that ganglion cells may be multinucleated, but the illustrations mostly show two nuclei giant cells.[1,2] Cibas makes a brief mention as well but offers no illustration.[3] The phenomenon does not even attract the attention of the AFIP Fascicles which aims to provide comprehensive illustrations for the covered entities.[4] Moreover, a Pubmed search on the subject did not generate much additional information.[5–10] Only rare cases could be located from internet sources. Only the European Federation of Cytology website (https://www.eurocytology.eu/course/paediatric-cytology/small-round-cell-lesions/neuroblastoma-

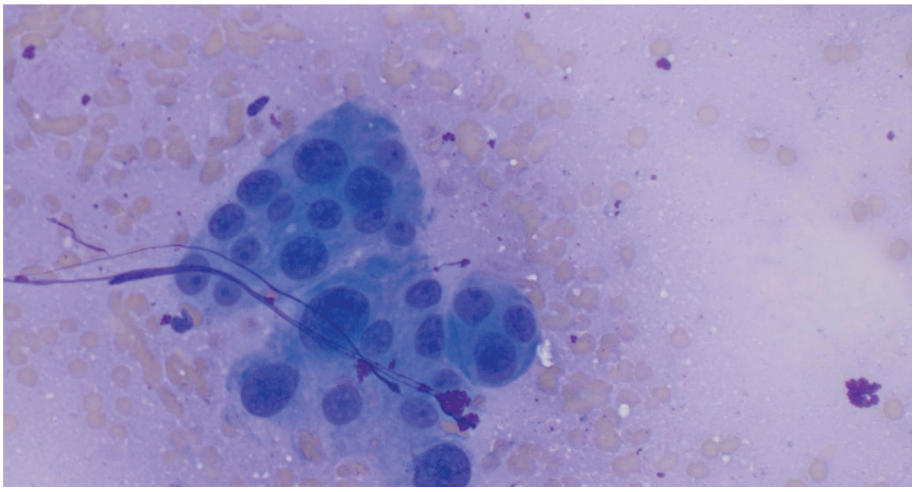

Fig. 2. Multinucleated giant cells are difficult to differentiate from osteoclast giant cells. Magnification: 400×.

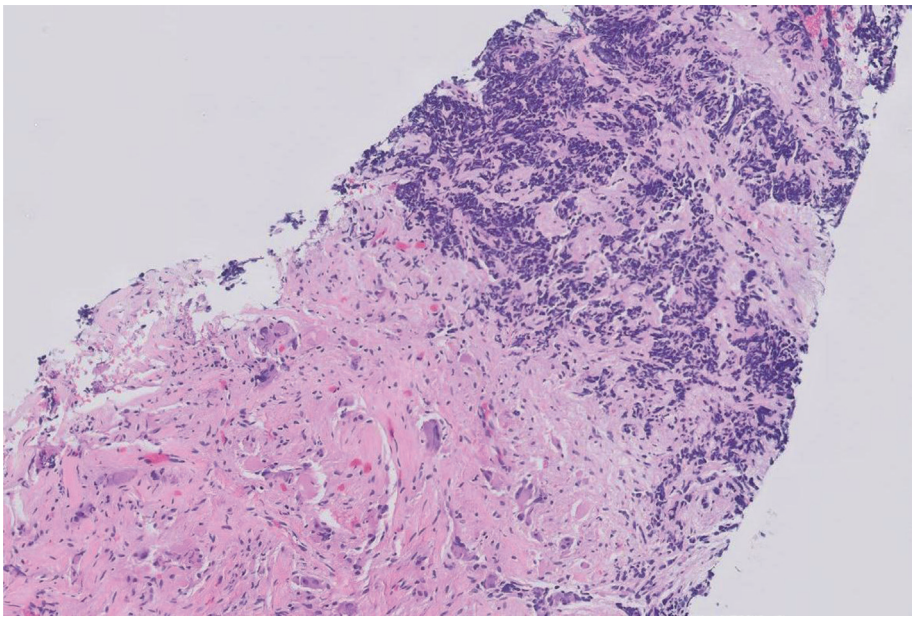

Fig. 3. Multinucleated giant cells are appreciated on regular H&E stained biopsy, mostly in more differentiated areas, i.e. favorable nodules. They are maturing neuroblasts or immature ganglion cells. Magnifications: 100×.

nos/) contains one better example (Fig. 6) and Dr. Syed Z. Ali on his Twitter account (https://x.com/sza_jhcyto/status/1197945525032538112?s=61&t=mjklwSQYUHBzs4yuvhFoDg) added one more. (Fig. 7).

There are several salient learning pointers in this case. 1) Despite its common presence in surgical specimens, multinucleation of maturing neuroblasts in ganglioneuroblastoma is an under-appreciated and under-reported phenomenon. However, in typical surgical pathology specimens, for experienced pediatric pathologists, the diagnosis is often sufficiently intuitive, such multinucleated giant cells do not particularly contribute to the clinching of the diagnosis. However, on cytology specimens, their contribution to a positive diagnosis could be immense. Note that neuroblasts observed are often

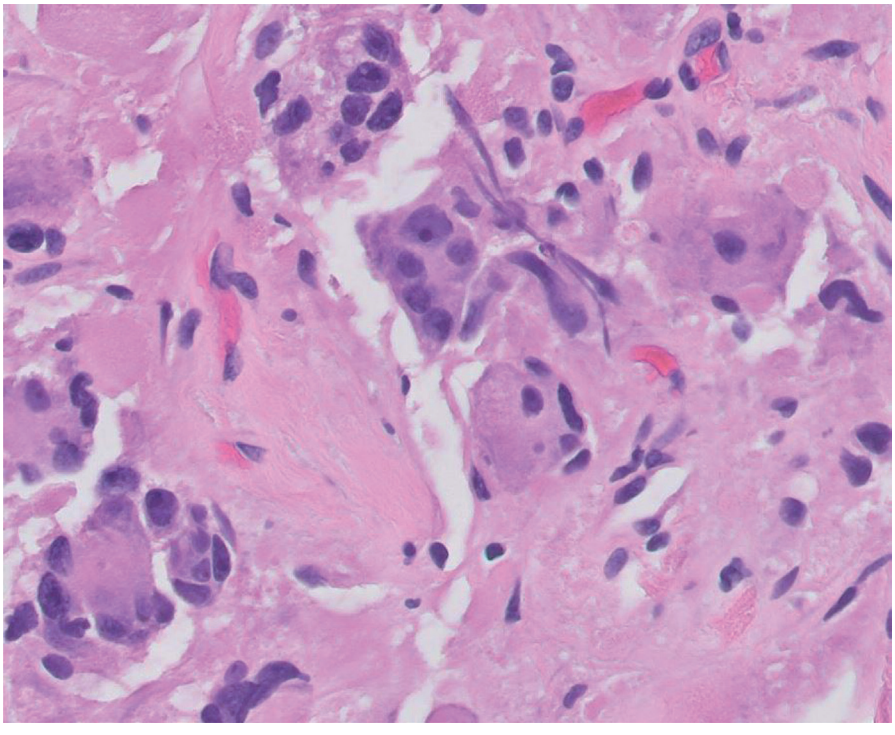

Fig. 4. Multinucleated giant cells are maturing neuroblasts or immature ganglion cells. While distinguishing between maturing neuroblasts and immature ganglion cells is difficult, the presence of satellite cells is a definitive marker of a cell being classified as a ganglion cell. Magnification: 200×.

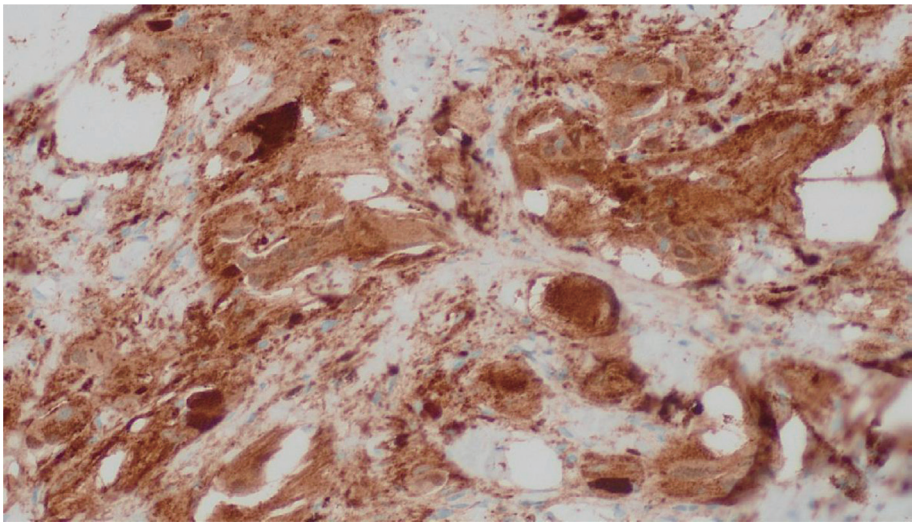

Fig. 5. Representative image of neuron-specific enolase staining slide. Magnification: 400×.

of varying degrees of maturation: They can be completely undifferentiated small uncommitted round cells or maturing neuroblasts with eccentric enlarged nuclei, small eosinophilic nucleoli, and ample well-defined cytoplasm with Nissl substance (also known as Nissl granules or tigroid substance) as well as vacuoles and scant cytoplasm. They can also reach immature ganglion cells showing frequent binucleation and multinucleation with eccentric huge nuclei and prominent eosinophilic nucleoli. A sophisticated diagnostic mind would entertain dynamic prototypical images of the entire range of these differentiations. 2) Skillfully recognizing this type of multinucleated giant cell is highly instrumental in interpreting cytology specimens, especially when the preparations have limited sampling, the architectural clues are absent, and when Homer Wright rosettes, neuropils, and microcalcification are only of specious presence. For general pathologists and cytopathologists alike, even for pediatric pathologists, such awareness is useful, particularly for intraoperative consultations. The correct diagnostic interpretation would assist faster clinical decisions and better allocation of limited sample materials. In this case, the allocation of limited material to an RPMI Medium for flow might be avoided retrospectively.

Finally, observation of giant cells prompts a wide range

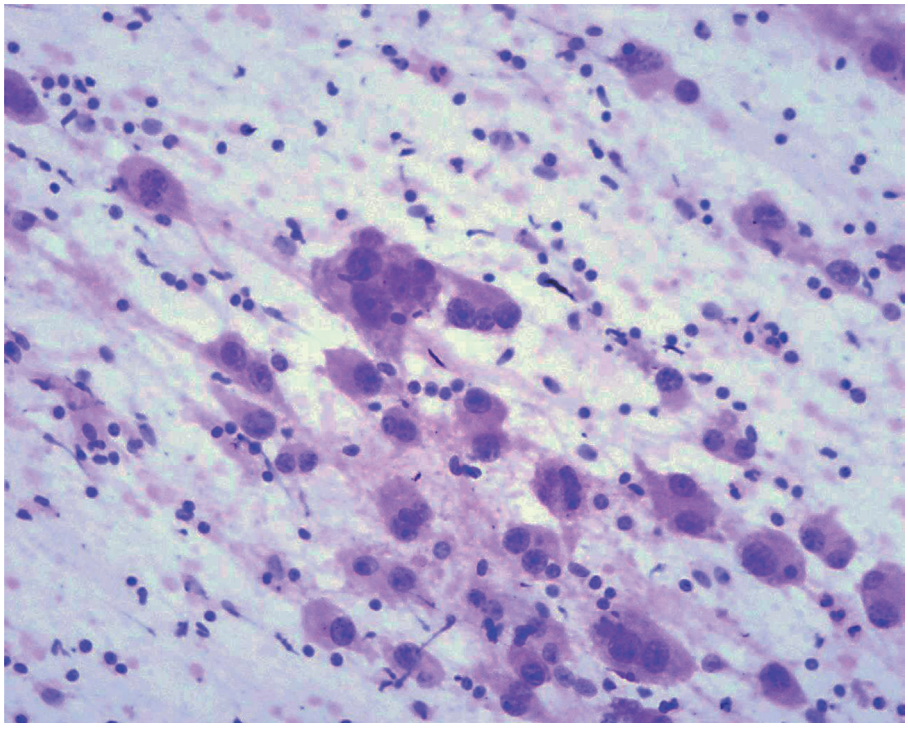

Fig. 6. Multinucleated ganglion cells from the website of European Federation of Cytology.

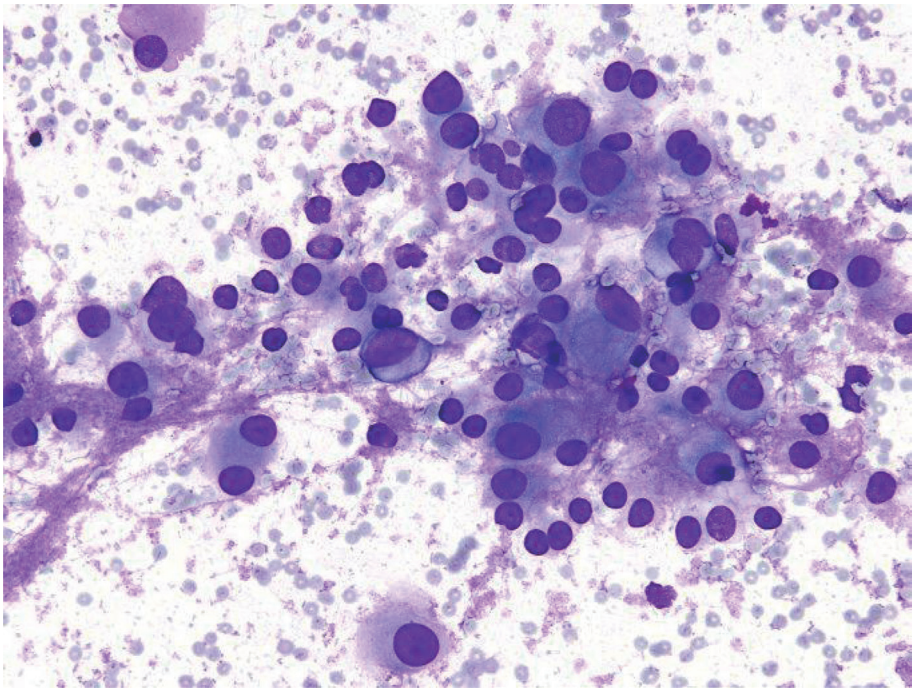

Fig. 7. Multinucleated ganglion cells from Internet source—Dr. Syed Z. Ali on his twitter account.

of differentials in tumor or tumor-like conditions. Although ganglioneuroblastoma diagnosis is made most frequently in the first 4 years of life, it is to be considered at all ages at any site—especially with more mature forms of ganglioneuromas—including many major sites such as the paravertebral space, mediastinum, and retroperitoneum.

A succinct survey-level knowledge deserves to have a place in a pathologist's diagnostic mindset. The first and most generic noticeable types are all macrophage-derived: Langhans-type is related to tuberculosis, syphilis, sarcoidosis, and deep fungal infections while epithelioid type in Crohn's disease is very closely related. Foreign-body giant cells form when a subject is exposed to a foreign substance. Also known as xanthelasma giant cells, Touton giant cells are epitomized by juvenile xanthogranuloma (JXG) and present also in lesions with a high lipid content such as fat necrosis, xanthoma, xanthelasma, xanthogranulomas, and occasionally dermatofibroma. Osteoclasts are found in bone lesions and varieties of other related lesions such as brown tumors of hyperparathyroidism and Paget's disease. The second group comprises tumor giant cells such as the following: those seen in anaplastic carcinomas and high-grade sarcomas including the wreath-like cells in rhabdomyosarcomas (not specific, they can be seen in other tumors, such as solid pseudopapillary tumors of the pancreas); floret cells in pleomorphic lipomas, liposarcomas, neurofibromas, and giant cell angiofibromas; syncytiotrophoblasts in choriocarcinomas; Reed-Sternberg cells in Hodgkin's disease; balloon cells in nevi and melanomas; and multinucleated giant cells in neuroendocrine tumors such as pheochromocytomas and medullary thyroid carcinomas, to which ganglioneuroblastoma type giant cells in this case belong. Outside these commonly mentioned, Aschoff giant cells in cardiac specimens, Warthin-Finkeldey giant cells, and Tzanck giant cells in viral infected cells deserve our attention in their own right. There have been many attempts to classify multinucleated giant cell lesions, and a recent review provided a snapshot of a different grouping in more detail.[11] For readers who are interested in the scientific insights into the most common macrophage-derived phenotypes of multinucleated giant cells, a good general review is supplied in a recent publication.[12] Surveying this knowledge suggests that multinucleated giant cells—albeit often providing us with diagnostic clues—can also be distractors, particularly epithelioid histiocytes and granulomas as well as occasional multinucleated giant cells, which are infrequent pathologic findings in lymphomas, Hodgkin lymphomas, and low-grade B-cell lymphomas.[13]

Conclusion

While the presence of multinucleated giant cells in neuroblastic tumor FNA is acknowledged, their proper illustration and diagnostic significance remain under-investigated. Addressing this knowledge gap through detailed morphological descriptions, comprehensive visual representations, and in-depth analyses of their clinical utility in bone and soft tissue tumors, neuroblastic tumors in particular, is crucial for improving diagnostic accuracy and patient management in this challenging area of cytopathology.

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Conflict of interest

The authors have no conflicts of interest related to this publication.

Author contributions

Study design and manuscript draft (JS); Critical revision and technical or material support (RF). All authors have made a significant contribution to this study and have approved the final manuscript.

Ethical statement

The study was performed following the ethical standards of the institutions to which we are affiliated and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report.

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