CASE REPORT

Metastatic alveolar rhabdomyosarcoma on the fine-needle aspiration cytology of cervical lymph node in an elderly patient, with FISH confirmation: A case report

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Abstract

Introduction: Alveolar rhabdomyosarcoma (RMS) usually occurs in adolescents and young adults, and most frequently arises in the extremities. *Case Report:* We present a rare case of metastatic alveolar RMS from a nasal primary to cervical lymph nodes (LNs) in an elderly patient, diagnosed on the fine-needle aspiration (FNA) biopsy. Smears showed malignant round cells featuring focal rhabdoid appearance, with rhabdomyoblastic differentiation further supported by immunocytochemical stains. Diagnosis of alveolar RMS was confirmed by fluorescence in situ hybridization (FISH) identifying FOXO1 gene involvement with dual colour break-apart probes at locus 13q14. *Discussion:* The differential diagnosis for a small round blue cell tumour in the elderly generally includes metastatic small cell carcinoma, lymphoma, malignant melanoma, RMS, desmoplastic small round cell tumour and Ewing's sarcoma/primitive neuroectodermal tumour. Subtle morphological analysis and expression pattern of immunostaining for skeletal muscle differentiation led to the diagnosis of RMS. Cytogenetic testing on the FOXO1 gene rearrangement helps definite subtyping of alveolar RMS.

Keywords: alveolar rhabdomyosarcoma, lymph node metastasis, fine-needle aspiration cytology

INTRODUCTION

Rhabdomyosarcoma (RMS) is the most common soft-tissue sarcoma of childhood, comprising approximately half of the pediatric malignancy overall. However, RMS is very rare, with an annual incidence of 4 to 7 per million children 15 years of age or younger.[1] On the other hand, RMS accounts for <3% of adult soft tissue sarcoma. With the use of modern combined modality therapy, 5-year overall survival (OS) of localised RMS exceeds 70% in children,[2] but is very poor in adult patients. A five-year OS for localized RMS and advanced RMS (with nodes and/or metastases) in adults was 43% and 5%, respectively.[3]

RMS generally has alveolar, embryonal, pleomorphic and spindle cell/sclerosing subtypes, according to WHO Classification of Tumours of Soft Tissue and Bone (4th edition). Alveolar RMS usually occurs in adolescents and young adults and arises most frequently in the extremities. RMS involving the head or neck region is more common in the case of embryonal subtype, predominantly affecting children and rarely involving regional lymph nodes (LNs).[4] Cytologic descriptions of RMS are mostly reported in malignant effusions. Studies of RMS in fine-needle aspiration (FNA) biopsies are infrequent.[5] Here, we report a rare case of an elderly patient with primary nasal alveolar RMS metastatic to the cervical LNs, diagnosed on FNA biopsy of the metastatic deposit.

CASE REPORT

A 76-year-old female patient, with a medical history of ischemic heart disease, hypertension, hyperlipidemia and diabetes mellitus, underwent FNA biopsy of a 0.9cm right cervical LN. Smears showed a high cellular yield of malignant round cells with marked variation in size and focal rhabdoid features (Figs. 1A-C). The majority of tumour cells had enlarged nuclei with irregular

nuclear contours and multiple small but visible nucleoli. The chromatin was delicate and open. The cytoplasm varied from minimal to abundant and was friable. Binucleation and multinucleation were frequently seen. Apoptosis and mitosis were present. Diff-Quik stains highlighted nuclear convolutions as well as the cells with abundant cytoplasm containing pink paranuclear material. Rhabdoid features were more prominent on the cell block. A minority of cells showed hyperchromatic nuclei with inconspicuous nucleoli. No strap cells were present. There was a low yield of mixed lymphoid cells in the background. No granulomas or necrosis were seen.

Retrospectively, the patient had been recently diagnosed of RMS. She presented with a feeling of right nasal obstruction associated with clear nasal discharge and pain around the right nasal bridge area for 3 weeks. She also complained of weight loss of 10-15 kg over the past 7 months. CT scan of paranasal sinuses revealed an infiltrative mass arising from the right nasal cavity, possibly a squamous cell carcinoma. The biopsy, however, showed morphological features which fell in the category of a small round blue cell tumour (Figs. 1D-F). The respiratory-type mucosa was infiltrated by densely packed clusters of malignant cells, featuring round to oval hyperchromatic nuclei with scant cytoplasm. Scattered cells with eosinophilic cytoplasm were intermixed. No cross striations or multinucleated tumour cells were noted. There were vague alternating cellular and myxoid areas with focal solid growth showing central discohesion of cells. Tumour cells were positive for desmin, myogenin, myoD1, CD56 and WT1, whilst being negative for AE1/3, S100, HMB45, CD45, synaptophysin and CD99 (not shown). It was diagnosed as rhabdomyosarcoma, while limited sampling precluded further subtyping.

Subsequent PET/CT investigation for tumour staging found hypermetabolic right cervical level II and left retropharyngeal LNs, suspicious for nodal disease. The right level II cervical LN was biopsied using FNA technique, revealing the previously described cytomorphology. Similarly, immunocytochemical stains of tumour cells in the LN showed skeletal muscle differentiation, featuring strong nuclear reaction for desmin, myogenin and myoD1 (Fig. 2). Negativity for MNF116 and melan-A ruled out metastatic carcinoma and malignant melanoma, respectively. CD45 only highlighted occasional lymphocytes in the background. Break-apart

of FOXO1 gene at 13q14 was demonstrated with fluorescence in-situ hybridization (FISH), performed on the cell block, which confirmed the diagnosis of alveolar RMS (Fig. 3).

The patient underwent 3-month neoadjuvant chemotherapy, resulting in an interval decrease of tumour size on the follow-up imaging. She underwent right subtotal maxillectomy and right modified radical neck dissection. The resection specimen revealed a small cell tumour with solid growth and focal vague alveolar architecture (Fig. 1G). Multinucleate tumour giant cells and prominent rhabdoid cytomorphology were focally seen (Figs. 1H-I). Metastatic tumour in the cervical lymph node was confirmed. There was focal involvement of resection margins by the tumour.

DISCUSSION

Sarcomas rarely spread via lymphatic route. RMS, especially of the lower extremities or of the head and neck region, is among the most common sarcomas with lymph node metastasis.[6] There is little literature on the cytologic diagnosis of metastatic alveolar RMS to lymph nodes, although cases to the thyroid gland, parotid gland and pancreas have been reported.[7-9] Alveolar RMS arising from the nasal vestibule with metastasis to cervical LNs as the first presentation was reported in a teenage girl.[10] Here, we add one similar case of metastatic alveolar RMS from a nasal primary to cervical LNs, but occurring in an elderly patient, which is rarer for this entity.

The biopsy of our patient showed a small round blue cell tumour. In her age group, differential diagnosis generally includes metastatic small cell carcinoma, lymphoma, malignant melanoma, and less likely RMS, desmoplastic small round cell tumour (DSRCT) and Ewing's sarcoma/primitive neuroectodermal tumour (PNET). In spite of a similar highly malignant morphology among these entities, subtle focal features provide a hint. Rhabdoid cells, in this case, suggested RMS, which was proved by diffusely and strongly positive staining with desmin, myogenin and myoD1. Negative staining with epithelial, melanocytic and lymphoid markers excluded the others. A strong cytoplasmic reaction with WT1 was present in our case as well as other previously reported RMS,[11] compared to nuclear staining in DSRCT. In addition, aberrant expression of CD56 seen in this case was also reported as a diagnostic pitfall of alveolar RMS.[12]
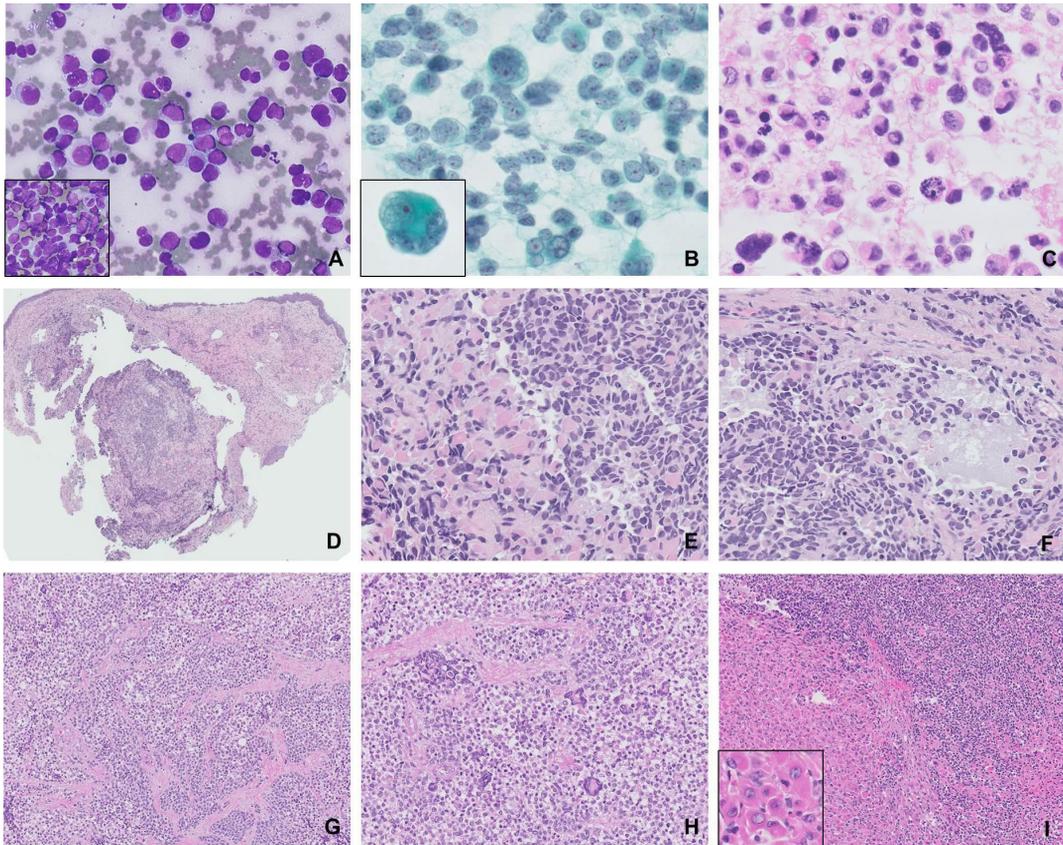
On histological examination, morphology

FIG. 1: Cytologic features of metastatic alveolar rhabdomyosarcoma and histologic correlation. Smears from fine-needle aspiration biopsy of the cervical lymph node showed singly dispersed (A, Diff-Quik stained, original magnification x200) and small loose clusters of (inset, x200) malignant cells with marked aniso-nucleosis. The majority of tumour cells showed enlarged hyperchromatic nuclei and conspicuous nuclei (B, Papanicolaou stained, x400), with frequent binucleation and multinucleation (inset, x400). Rhabdoid features were commonly seen (C, H&E, x400). The biopsy of primary sinonasal mass showed infiltrative clusters of malignant cells underlying respiratory-type mucosa (D, x20). Dual population of primitive ovoid cells and rhabdoid cells was observed (E, x200). Focal solid growth showed central discohesion of cells (F, x200). Resection after neoadjuvant chemotherapy revealed tumour with alveolar pattern separated by fibrous septae (G, x50) and frequent multinucleated tumour giant cells (H, x100). Again, present were solid areas with both primitive-looking tumour cells (I, x50) and those with prominent rhabdoid differentiation (inset, x200).

alone, when classical, helps subtyping of RMS. However, a reliable subclassification of RMS cannot be made from FNA smears.[13] Cytologic features of RMS overlap while slightly differing in its subtypes. A few large series tried to characterize the cytologic features of RMS on the FNA biopsy, including 301 cases, among which 145 were alveolar RMS.[5,13-16] Most of RMS share certain features such as high cellularity, predominant single cells with occasional ill-defined clusters and small round blue cell appearance.[5] Usually, tumour cells from alveolar RMS are larger compared to those from the embryonal subtype, with coarse chromatin and small nucleoli. Binucleation and multinucleation are more commonly seen. A variable amount of mucoid to necrotic background is observed.[5] In embryonal RMS, there is a mixture of spindle and small round cells with fine chromatin and inconspicuous nucleoli.[7] Other subtypes of RMS are rare and their cytologic features were seldom described. Pleomorphic RMS displays marked pleomorphism and large rhabdoid cells.[17] Dense sclerotic background is typically seen in spindle cell/sclerosing RMS.[18]

Cytogenetic testing helps definite subtyping. Most cases of alveolar RMS harbour either t(2;13) or t(1;13) translocation, resulting in PAX3-FOXO1 and PAX7-FOXO1 fusion genes respectively, while embryonal, pleomorphic and
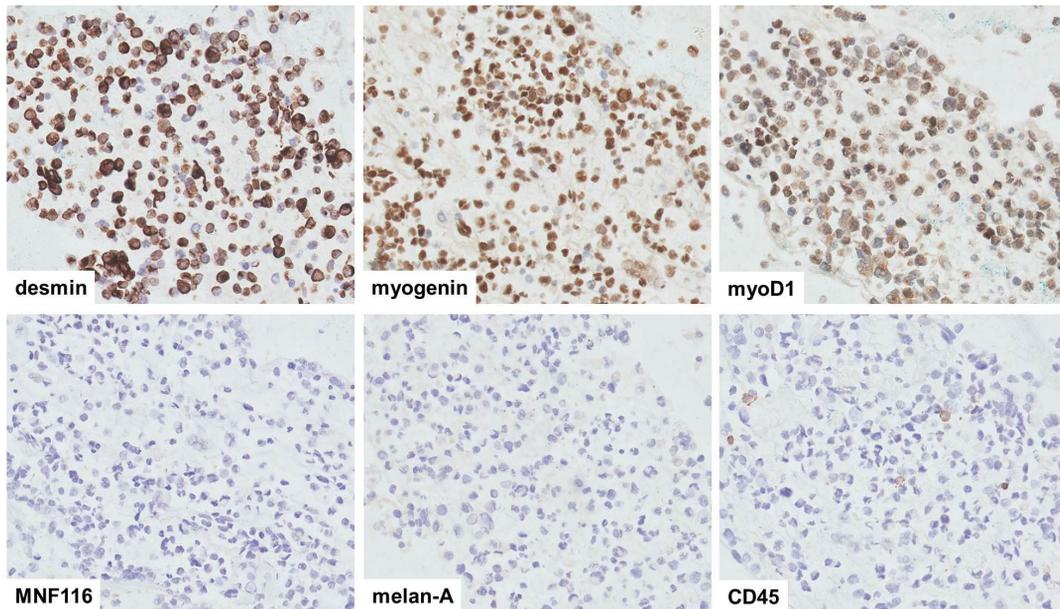
FIG. 2: Immunocytochemical stains of fine-needle aspiration biopsy of the right cervical lymph node. Tumour cells showed strong nuclear reaction for desmin, myogenin and myoD1, with negativity for MNF116 and melan-A. CD45 only highlighted occasional lymphocytes in the background.

spindle cell/sclerosing subtypes typically do not have such molecular changes. The break-apart of FOXO1 gene at locus 13q14 demonstrated by FISH in this case, confirmed the diagnosis of alveolar RMS.

This patient was also incidentally found to have a 3.6 cm dominant solid mass in the right lobe of thyroid gland, with small cysts and nodules in the left lobe. Albeit extremely rare, metastatic alveolar RMS in the thyroid has been reported.[7] FNA biopsy of the right thyroid mass showed a follicular lesion with a microfollicular pattern and absence of colloid, which was suspicious for a neoplasm of thyroid
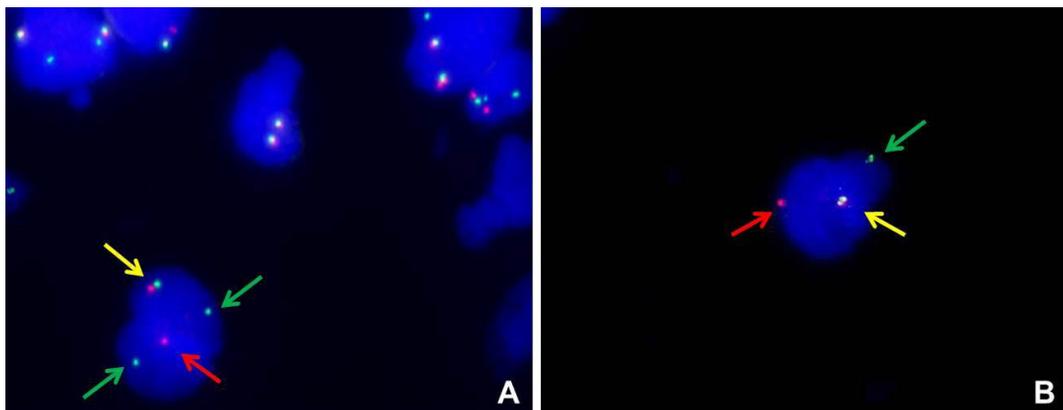

FIG. 3: Fluorescence in situ hybridization (FISH) on FOXO1 gene performed on the sample from right cervical lymph node. FOXO1 dual colour break-apart probes (Abbott Molecular, Abbott Park, Illinois) were used for the detection, consisting of a 720kb probe labeled with SpectrumGreen™ fluorophore that lies proximal to the FOXO1 gene and a 650kb probe labeled with SpectrumOrange™ fluorophore distal to the FOXO1 gene at 13q14. An atypical FISH signal pattern consisting of one fusion (yellow arrow), one red (red arrow) and two green (green arrow) signals was observed in 98% of 200 nuclei scored, indicating disruption of the FOXO1 gene (A). The presence of an extra 3' FOXO1 gene segment might indicate either gain of an extra 3' FOXO1 gene segment or further disruption of the rearranged 3' FOXO1 gene leading to two copies of green signals. Another minor signal pattern consisting of one fusion, one red and one green signals was also observed, indicating disruption of the FOXO1 gene at 13q14 (B).

origin. Total thyroidectomy was performed at the same setting of maxillectomy. The right thyroid mass turned out to be an adenomatous nodule with an additional incidental finding of papillary microcarcinoma.

Prominent rhabdoid differentiation was focally seen in the resection specimen. This chemotherapy-induced cytological maturation was thought to be a sign of an active, persistent tumour. Furthermore, in the head and neck region, RMS involving the paramengingeal area including nose and sinuses, is considered to have a worse prognosis compared to the orbit and other sites.[19] The patient had local recurrence a month after surgery, and underwent further adjuvant chemotherapy and palliative radiotherapy. The patient deceased from the disease 16 months after the initial diagnosis.

In conclusion, alveolar RMS is a highly malignant tumour, with rare LN involvement. A combination of morphology, immunological staining and genetic testing helps the diagnosis of alveolar RMS and distinguishes it from other entities.

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