

CASE REPORT

Primary sinonasal Ewing sarcoma: A case report

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Abstract

Background: Ewing sarcoma (ES) is an aggressive tumour which is typically skeletal in origin. ES involving the head and neck region is uncommon and can be easily confused with other small round blue cell tumours. We herein present a rare case of ES involving the sinonasal area. **Case presentation:** A 5-year-old Somali boy with no known medical illness presented with progressive nasal blockage associated with clear nasal discharge and intermittent spontaneous epistaxis for three months. CT paranasal sinus and neck region revealed poorly enhancing expansile mass in the right maxillary sinus with areas of necrosis within. Initial radiological differential diagnoses were lymphoma and rhabdomyosarcoma. The mass was biopsied and histologically showed diffuse sheets of small round blue cells that was positive to CD99, NSE and vimentin. The muscle and lymphoid markers were negative. Fluorescence in-situ hybridisation (FISH) study revealed the presence of *EWSR1* gene rearrangement thus diagnosis of ES was rendered. **Conclusions:** ES of sinonasal tract is a rare entity and its pathological features significantly overlap with others small round blue cells tumour. Demonstration of *EWSR1* gene translocation is recommended for the diagnosis of ES particularly at uncommon sites.

Keywords: Sinonasal tract, sinonasal tumour, Ewing sarcoma, *EWSR1* gene rearrangement

INTRODUCTION

Ewing sarcoma (ES) accounts for 6-8% of primary bone tumour.¹ It is typically seen in the long bones of extremities. Head and neck origin of this tumour is rarely observed (1-4% of all ES) with sinonasal ES forms another uncommon subset.² ES of the head and neck may be difficult to diagnose as they display significant histologic overlap with other more common undifferentiated small blue round cell malignancies. Therefore, additional investigations including evaluation of *EWSR1* gene rearrangement to confirm the diagnosis of ES are essential particularly at the uncommon sites. Presence of the above gene rearrangement is the hallmark of ES which complement the clinical, radiological, histological and immunohistochemical assessments.

CASE REPORT

A 5-year-old Somali boy with no known medical illness presented to a hospital in Somalia with progressive nasal blockage associated with clear nasal discharge and intermittent spontaneous epistaxis for three months. There was no history of foreign body insertion, foul-smelling nasal discharge or visual abnormalities. An initial paranasal sinus computed tomography (CT) scan done at a hospital in Somalia reported as a benign nasal tumour.

Subsequently, the parents decided to seek a second opinion at our centre. Further assessment revealed that there was no cervical lymphadenopathy or hepatosplenomegaly. The cranial nerves were intact. Anterior rhinoscopy showed a pink mass covered by slough occupying the whole right nasal cavity with clear secretions

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(FIG 1). The left nasal cavity was unremarkable.

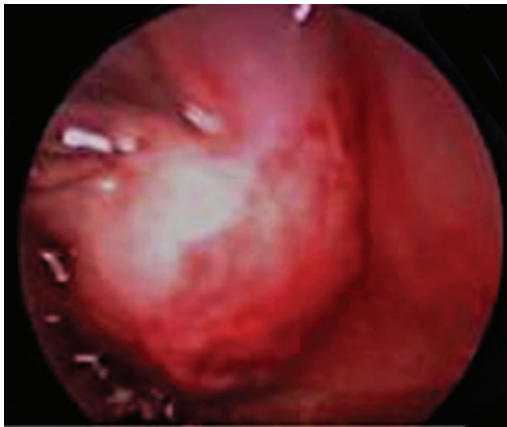


FIG. 1: Right nasal cavity mass on anterior rhinoscopy

Computed tomography (CT) scan of the paranasal sinus and neck region revealed poorly enhancing expansile mass in the right maxillary sinus with areas of necrosis within. The mass encroaches into the right sinonasal, right ethmoid and sphenoid sinuses, and the right nasopharyngeal space. There was erosion of the medial, lateral walls and floor of the right maxillary sinus. The right pterygoid plate was eroded and the right pterygopalatine fossa (PPF) was obliterated by the mass. No obvious calcification or aggressive periosteal reaction seen. CT angiography (CTA) further revealed a poorly vascular nature of the mass which excluded juvenile nasopharyngeal angiofibroma (FIG 2). Magnetic resonance imaging (MRI) of the paranasal area exhibited the solid-cystic nature of the mass, best seen

on T2-weighted imaging, with heterogeneous enhancement post-Gadolinium and invasion of the right infratemporal space, poor fat content as well as restricted diffusion seen on DWI and ADC sequences. It also shows invasion into the right orbital apex (FIG 3). There was no evidence of distant metastasis seen in MR whole body imaging. The radiological diagnosis based on imaging was either lymphoma or rhabdomyosarcoma since these diagnoses are more common in this age group.

He subsequently underwent a biopsy of the nasal mass. Histopathological evaluation revealed small blue cell tumour arranged in diffuse sheets (FIG 4A) displaying monomorphic, hyperchromatic nuclei, inconspicuous nucleoli and scanty eosinophilic cytoplasm. Some of these cells are forming rosettes. Panels of immunohistochemical tests were done showing the neoplastic cells were positive for CD99 (FIG 4B), NSE and vimentin. The neoplastic cells were negative for epithelial marker CK MNF, lymphoid and immature lymphoid markers (CD45 and TdT), neuroendocrine markers (synaptophysin and chromogranin) and S100. The muscle markers, SMA and desmin were also negative however MYOD1 was inconclusive. Special stains with PAS showed presence of glycogen in some of the neoplastic cells (FIG 4C and D). Molecular study by fluorescence in-situ hybridisation (FISH) study using break apart probe had shown presence of split signals within the tumour cells, consistent with EWSR1 gene rearrangement (FIG 5). Thus, the final diagnosis of Ewing sarcoma was rendered.



FIG. 2: (A) Axial cut of contrast-enhanced CT, (B) bone-reconstruction CT, and (C) CT angiography. The mass in the right maxillary sinus is poorly enhanced with areas of hypodensity within suggestive of necrosis. The tumour is seen encroaching the right nasopharyngeal space posteriorly, sinonasal tract medially and invasion of the right pterygopalatine fossa (A, white asterisk). There is associated bone erosion involving the medial and lateral wall of the right maxillary sinus (B, white arrow). CTA shows a poorly vascularised tumour, making the diagnosis of juvenile nasopharyngeal angiofibroma less likely (C, black asterisk).

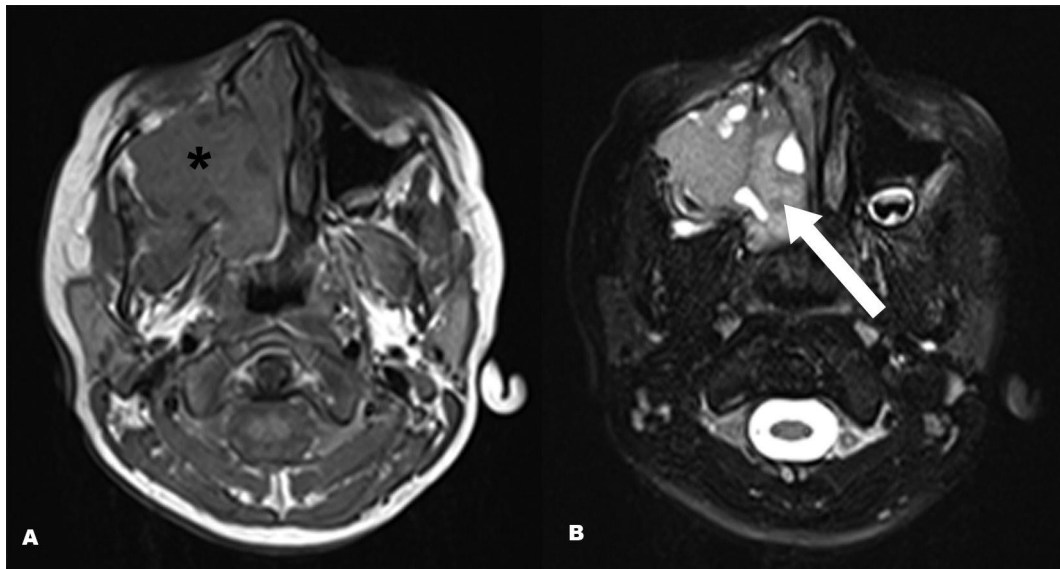


FIG. 3: (A) T1-weighted and (B) T2-weighted fat-saturated images at the level of nasopharynx. It is seen that the right maxillary tumour has hypointense to isointense signal on T1-weighted (*black asterisk*) and areas of high T2-weighted within the tumour suggestive of necrosis (*white arrow*).

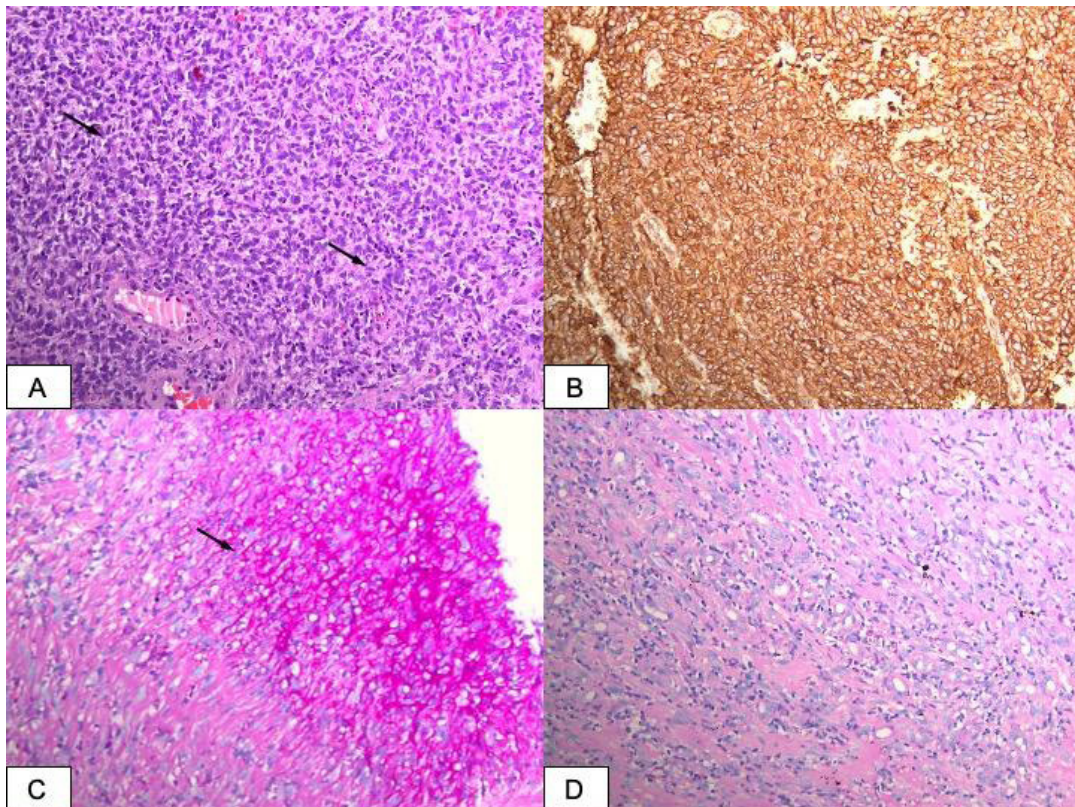


FIG. 4: Histopathological evaluation of the biopsy of nasal mass. A. The nasal mass is composed of small round blue cells arranged in diffuse sheets with occasional rosettes formation seen (arrow) (Hematoxylin and eosin, 200x magnification). B. The malignant cells are diffusely positive for CD99 (200x magnification). C. Presence of magenta-coloured glycogen was demonstrated within some of the malignant cells (arrow) which was digested and became colourless after treatment with diastase (D) (200 x magnification).

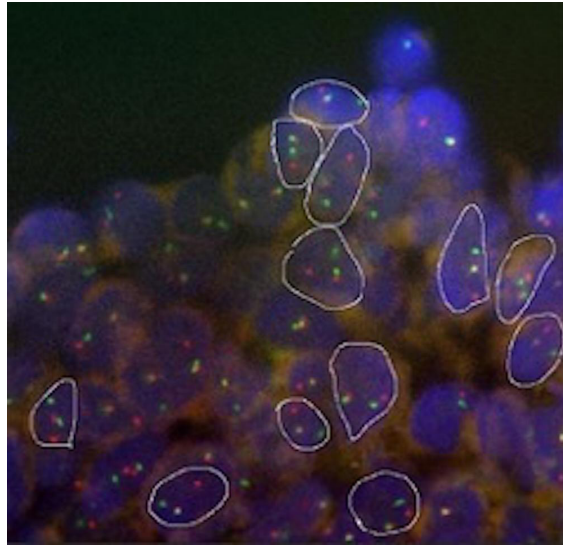


FIG. 5: Fluorescence in situ hybridization (FISH) study using break-apart probe showed presence of split signals within the malignant cells (circled cells). FIG. 5: Fluorescence in situ hybridization (FISH) study using break-apart probe showed presence of split signals within the malignant cells (circled cells).

He was then referred to an oncologist for chemotherapy. Bone marrow biopsy was performed before the start of chemotherapy which shows no evidence of metastatic disease within the marrow. He was started on induction chemotherapy consisting of vincristine, ifosfamide, doxorubicin and etoposide planned for 6 courses, 21 days in between based on Euro Ewing 2012 protocol. Later, a follow-up MRI

showed significant reduction of the tumour as well as improvement in local invasion after three courses of chemotherapy (FIG 6).

DISCUSSION

ES is a malignant small round blue cell tumour arising from primitive neuroectodermal cells. It was first described by James R. Ewing in 1921.³

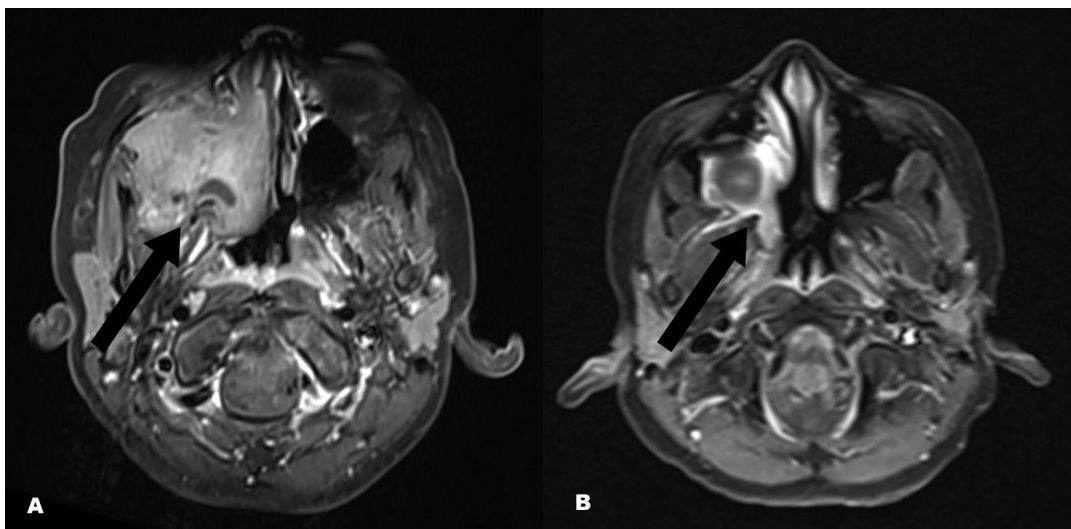


FIG. 6: Contrast-enhanced T1 weighted (A) before chemotherapy (*black arrow*) and (B) after 3rd cycle of chemotherapy (*black arrow*) shows significant reduction of tumour size and its mass effect. The tumour in (B) shows more peripheral enhancement with poor enhancement centrally in comparison with pre-chemotherapy in (A).

It usually involves the long bones of extremities, less commonly pelvis, ribs, skull, vertebra, scapula, and short tubular bones of hands and feet.¹ It commonly affects children and young adults, with 80% of cases occurs before the age of 20 years old.¹

About 10-20% of ES cases are extraskeletal.¹ Head and neck ES is rare.² Therefore, other more common tumour with small round blue cell morphology such as rhabdomyosarcoma, olfactory neuroblastoma, lymphoma, mucosal melanoma, squamous cell carcinoma, NUT carcinoma, sinonasal undifferentiated carcinoma, neuroendocrine carcinoma, pituitary adenoma, mesenchymal chondrosarcoma, small cell osteosarcoma and plasmacytoma should be excluded first (Table 1).⁴

Radiologically, there are many overlapping features between benign and malignant soft tissue tumours of the head and neck rendering diagnosis exceptionally difficult based on imaging alone.⁵ There are no specific or typical features of extraskeletal Ewing sarcoma on CT and MRI, that can be differentiated from other sinonasal tumours. Previous literature described that extraskeletal Ewing sarcoma as heterogeneously enhancing masses and usually associated with local invasion. The tumour will also show mass effect by displacing surrounding structures and invasion of the nasal septum, turbinate and skull, and occupying the anterior cranial fossa.⁶ This is evident in our case, which showed locally aggressive tumour of the right maxillary sinus with mass effect. On CT, it usually presents as soft tissue mass with similar attenuation to muscle. The majority shows heterogeneous enhancement with central hypodensities in keeping with necrosis, which can be seen in our patient. Intratumoural haemorrhage may occur and present as high-density foci.^{5,6} Although calcification is a feature of Ewing sarcoma, it was not present in our case. Furthermore, there is absence of haemorrhagic component which can also be seen in ES. Nevertheless, calcification is not a diagnostic imaging feature of Ewing sarcoma. It can also be found in undifferentiated carcinoma.⁵

On MRI, this tumour is generally hypointense to isointense on T1-weighted images and hyperintense on T2-weighted images. Following Gadolinium administration, it typically shows heterogeneous enhancement.² Our patient had a solid-cystic component which explains the heterogeneity in T1-weighted and T2-weighted images. Certain imaging features can lead

towards malignancy such as ill-defined margins, heterogeneous signals in MRI and an increasing size and depth. Restricted diffusion as well as high uptake values on PET are also features that can point towards malignancy. CT and MRI are valuable in determining local invasion and distant metastasis. However, imaging alone is insufficient for differentiating sarcoma since no specific imaging findings will point to the diagnosis of ES.⁵

In practice, the various types of primitive small round blue cell tumours usually appear undifferentiated and in most instances the samples taken particularly from sinonasal areas are scanty. Thus, these factors pose difficulty in obtaining definitive diagnosis of primitive tumour within the head and neck area without the help of ancillary tests.

Histologically, ES is also composed of undifferentiated uniform small round cells, absence of nucleoli, finely granular chromatin pattern and scanty cytoplasm with varying degrees of neuroectodermal differentiation.¹ These neuroectodermal differentiation comprises of medium sized cells oriented toward a central space forming a rosette.⁴ Therefore, it is necessary to select a panel of immunohistochemical studies during the initial histopathological assessment to avoid misclassification. The majority of the cells contain glycogen which is demonstrated by PAS positive with diastase digestion.¹ Initial panel of immunohistochemical studies may include an epithelial marker (pancytokeratin such as CKAE1/AE3, epithelial membrane antigen or OSCAR), a neuroendocrine marker (synaptophysin, chromogranin, or CD56), a muscle marker (desmin, myogenin, MYOD1), S100 (to exclude melanoma) and CD45 (to exclude lymphoma).⁴ The pattern of reactivity will then help to direct additional immunohistochemical (IHC) studies in conjunction with histological features, clinical and imaging findings as indicated (Table 1). In our case, SMA and desmin were negative nevertheless MYOD1 was inconclusive. Given one of the initial radiological diagnosis was rhabdomyosarcoma, EWSR1 gene translocation is needed to confirm the diagnosis of ES.

Additional second panels of immunohistochemical studies include CD99 and FLI-1. CD99 typically shows diffuse positivity to CD99 however, its positivity is not specific and can be seen in a lot of other neoplastic conditions.^{1,4} Although FLI-1 immunohistochemistry is typically positive in ES (about 75% of cases), it is also non-specific. FLI1-positivity should

Table 1: Morphology and immunoprofile of small round blue cells tumour of head and neck

	Mucosal melanoma	Rhabdomyosarcoma	Sinonasal undifferentiated carcinoma	NUT	Neuroendocrine carcinoma	Extranodal NK/T cell lymphoma nasal type	Olfactory neuroblastoma	Ewing Sarcoma
Pattern	Protean, solid, organoid, fascicular ⁴	Sheets, alveolar ⁴	Sheets, nests ⁴	Sheets, nests ⁴	Syncytial, islands, ribbons, sheets ⁴	Diffuse ⁴	Lobular ⁴	Sheets, nests ⁴
Morphological features	Large, polygonal, epithelioid, rhabdoid, plasmacytoid, spindle cells; pigment, pleomorphism, high mitotic count, limited necrosis, rare vascular invasion, no neurofibrillary matrix ⁴	Round, strap, spindled, rhabdomyoblasts, primitive cells, pleomorphism present, variable mitoses, limited necrosis, rare vascular invasion, no neurofibrillary matrix or rosettes ⁴	Medium cells, inconspicuous nucleoli, pleomorphism, high mitotic count, prominent necrosis, lympho-vascular invasion, no neurofibrillary stroma, pseudorosettes usually absent ⁴	Medium cells, monotonous, high nuclear ratio, abrupt keratinization or squamous differentiation, high mitotic count, tumour necrosis ⁴	Small cells, with high nuclear:cytoplasmic ratio, nuclear molding, nuclei crushed, moderate pleomorphism, inconspicuous nucleoli, high mitotic count, no neurofibrillary matrix, pseudorosettes may present ⁴	Polymorphous, small to large cells, folded, cleaved and grooved nuclei, pleomorphism, high mitotic count, necrosis, angiocentric, angiodestructive, no neurofibrillary matrix or rosettes ⁴	Salt-and-pepper chromatin, small nucleoli (grade dependent), limited mitoses, scant necrosis, neurofibrillary matrix present, pseudorosettes and true rosettes ⁴	Uniform, Medium, round cells, fine chromatin, vacuolated cytoplasm often containing glycogen, high mitotic count, necrosis, rosettes often present, no neurofibrillary matrix ⁴ .
Typical IHC positivity	S100, SOX10, HMB45 ⁴	Desmin, myogenin, MYOD1 ⁴	Pan-CK, p16, CD117, CK7 (~50%), EMA (~50%) ⁴	Pan-CK, NUT IHC, p16, CK5/6 ⁴	Synaptophysin, chromogranin, CD56, NSE ⁴	CD45, CD3, EBER-ISH (100%) ⁴	Synaptophysin, chromogranin, CD56, NSE, S100 (sustentacular cells only), GFAP (sustentacular cells only), SOX10 (sustentacular cells only) ⁴	CD99, FLI-1 (~75%), NSE ⁴

not be considered diagnostic for ES as it can also be positive in other small round blue cells tumour affecting the sinonasal area such as mucosal melanoma, rhabdomyosarcoma and neuroendocrine carcinoma.⁴ Thus, EWSR1 gene translocation study is important in the diagnosis of ES at uncommon sites such as sinonasal area.

Almost all cases of ES showed translocation of EWSR1 gene on chromosome 22 and a member of the ETS family of transcription factors.¹ In about 85-90% of ES cases, there is a translocation t(11;22)(q24;q12) that fuses Ewing's sarcoma gene (EWS), and friend leukaemia virus integration site 1 gene (FLI-1).^{1,2} The diagnosis of ES is confirmed by the presence of a positive RT-PCR result, or supported by a split EWSR1 FISH signal.¹ Even though these methods confirmed the presence of EWSR1 gene translocation, it does not identify the translocation partner.^{1,4}

Although EWSR1 gene translocation is the hallmark of ES, the same findings may be observed in other soft tissue tumour including desmoplastic small round cell tumour (DSRCT), myxoid liposarcoma (MLPS), extraskelatal myxoid chondrosarcoma (EMC), angiomatoid fibrous histiocytooma (AFH), clear cell sarcoma (CCS) and myoepithelial neoplasms.⁷ Among these tumours, only DSRCT shows small round blue cells morphology, but it is extremely rare in sinonasal area. DSRCT is usually positive for cytokeratin, desmin and NSE.⁸ In our case, the neoplastic cells are negative for cytokeratin and desmin. Therefore, molecular studies should not be used alone in diagnosing ES. It should be done in conjunction with morphological and immunohistochemical assessment.

Anderton *et al.* had proposed Euro Ewing 2012 protocol for treatment of ES based on age at diagnosis, disease status (localised disease, presence of lymph nodes or distant metastasis) and volume of tumour at diagnosis.⁹ With the current multimodal therapy including combined chemotherapy, surgery and radiotherapy, a localised ES has a 5-year survival rate of about 65% with a 3-year event-free survival (EFS) in 30% patients with ES and lung-only metastases. This tumour showed very poor prognosis in patients with disseminated disease demonstrating with overall survival (OS) at 3 years of only 29%.⁹

CONCLUSION

ES of sinonasal tract is a rare entity and its pathological features significantly overlap with

other small round blue cells tumours which may pose a great diagnostic difficulty. Demonstration of EWSR1 gene translocation is recommended for the diagnosis of ES particularly in uncommon areas such as sinonasal tract.

ACKNOWLEDGEMENT

Authors' contribution: All authors contributed to the final preparation of the manuscript. MFA involved in drafting the manuscript. AA involved in clinical and surgical management of the patient. MIA & FMZ involved in radiological imaging and provided the radiological images and report. SHMP and AA involved in editing the final draft of the manuscript.

Conflict of interest: The authors declare no conflict of interest.

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