Case reports

Adamantinoma-like Ewing Sarcoma: A Report of two rare cases in the pancreatic tail and spine

Abstract:

Adamantinoma-like Ewing sarcoma (ALES), an extremely rare variant of Ewings sarcoma occurs primarily in the head and neck sites. ALES is characterized by basaloid cytomorphology, immunohistochemically expresses keratins, p63, p40, CD99, and harbors t (11; 22) EWSR1::FLI1 translocation on fluorescence in situ hybridization (FISH). The current case report discusses two cases of ALES, one in the pancreatic tail of a 64-year-old male and the second in the lumbar spine of an 18 yr old male. The IHC for both cases showed similar picture, confirming ALES through Fluorescence in situ hybridization (FISH), which indicated EWSR1 gene rearrangement. ALES being relatively rare and aggressive, diagnosis and the treatment poses significant challenges. Diagnosis relies on morphological, immunohistochemical, and molecular findings.The diagnostic findings helped in establishing a diagnosis of sarcoma which could have easily been misdiagnosed as a carcinoma. Thus aiding appropriate selection of therapeutic strategies. Due to its rarity, further research is necessary to improve diagnostic accuracy and treatment outcomes.

Key words: Ewing Sarcoma, Adamantinoma, fluorescence in situ hybridization, lumbar spine

Introduction:

Ewing sarcoma (ES) is a tumour predominantly afflicting adolescents, and is the second most prevalent primary malignant bone tumor. Adamantinoma-like Ewing sarcoma (ALES) initially described by Bridge et al in 1999, is an extremely rare variant of Ewing sarcoma [1]. It accounts for <5% of Ewings Sarcoma and predominantly occurred in the head and neck sites [2]. Histologically, ALES exhibits basaloid cytomorphology, expresses keratins, p63, p40, and CD99, and harbors the t (11; 22) EWSR1::FLI1 translocation. Immunohistochemically, ALES shows strong expression of keratins 5, AE1/AE3, CAM5.2, p63, p40, and p16, with retained INI1 expression. ALES may also exhibit features like infiltrative growth patterns, high-grade histological characteristics and sudden keratinization. These may vary with the site of occurrence. ALES may at times mimic other malignancies; hence, molecular studies are necessary to avoid potential errors in diagnosis. A thorough understanding of the unique histological and molecular features is thus, essential for the diagnosis and appropriate management of ALES [3]. However, due to the rarity of ALES, there is paucity of literature to guide the treatment and related outcomes.

Case presentation

Case 1:

A 64-yr-old male, presented with epigastric pain of unknown duration. He underwent a computed tomography (CT) scan, which suggested a splenic abscess. The patient was operated for distal pancreatico-splenectomy. The specimen measured 12 x 6 x 10.5 cm. The external surface was congested and bulky. The capsule was ruptured at the inferior surface. Cut section revealed multiple brownish firm lesions ranging from 0.5 to 2 cm in diameter. At the hilum, pancreatic tissue was seen with a whitish to yellowish firm lesion measuring 3.5 x 2.2 x 1.6 cm.

Serum tumour markers were within normal limits. The original histopathology report revealed a malignant small round cell tumour in the tail of pancreas, involving hilar fibro adipose tissue and adjacent spleen [Fig 1-2]. The case was received at our laboratory for IHC studies for confirmation and categorization.

The differentials we considered were poorly differentiated squamous cell carcinoma, Neuroendocrine tumor, Adenosquamous carcinoma – basaloid type, Desmoplastic small round cell tumor (DSRCT), metastasis and a rare possibility of Ewing sarcoma /PNET.

Keeping these in mind an IHC panel was ordered. The tumour cells were positive for Pan CK, p40, p63, CD99, NKX2.2 and FLI1 with an intermediate to high Ki-67 index. They were negative for Synaptophysin, Chromogranin,CK7, CK20 , CEA, WT1,EMA, NSE, Desmin, Vimentin , CA19.9,PSA, TTF-1, Uroplakin, GATA3, NKX3.1, SMA, and CD117 [Fig 3-7]. These results, along with the morphology of a round cell tumor and certain nests showing central keratinization, helped us rule out the aforementioned differentials and narrow down our diagnosis to Adamantinoma like Ewing sarcoma. Despite this, there was a disagreement in house and hence we decided to carry out FISH studies in order to confirm the findings. Fluorescence in situ hybridization (FISH) examination revealed Interphase cells showing EWSR1 gene t (22q12) rearrangement positive.

Based on the morphological, immunohistochemical, and molecular findings, we arrived at a diagnosis of *Adamantinoma-like Ewing Sarcoma Family of Tumors* of the pancreatic tail.

Post-operative follow up was uneventful and subsequently the patient was lost to follow up.

Case 2:

The second case was of a 16-year-old male patient who presented with complaints of recurrent lower back pain for the past few months. The patient was evaluated for his lower backache and underwent a MRI scan of the lumbar spine. The MRI findings revealed altered signal intensity involving the lower dorsal and lumbar vertebras. PET CT scan findings were highly suspicious for primary multicentric skeletal lymphoma. Other less likely differentials include primary multicentric skeletal tuberculosis. Rest of the scan findings were negative for any FDG avid significant hypermetabolic pathology in the regions surveyed. On the basis of above findings, L1 vertebral lesion was sent for biopsy suspecting a malignancy. On gross examination, two linear bony cores measuring 0.4 and 0.5 cm were received and processed [Fig 8-10]. On microscopy, serial sections of biopsy showed mature bony trabeculae showing involvement by a malignant tumor. The tumor cells were arranged in sheets. Individual tumor cells had pleomorphic, hyperchromatic nuclei with occasional prominent nucleoli. L1 vertebral lesion biopsy was thus positive for malignancy. Hence an IHC panel was requested. The working differentials were of an Ewing Sarcoma, considering the age and site, a lymphoma and a possibility of a neuroendocrine carcinoma. The tumour cells were positive for Vimentin, Pan CK, p40, p63, CD99, NKX2.2, while weakly positive for synaptophysin and chromogranin [Fig 11-15]. They were negative for Desmin, LCA, myogenin. The Ki-67 was intermediate index. Hence, in accordance to the morphology and IHC panel a diagnosis of Adamantinoma like Ewing sarcoma

was offered. Molecular confirmation was carried out which showed a break in the EWS gene, thereby confirming our diagnosis [Fig 16].

Discussion

Adamantinoma-like Ewing sarcoma (ALES) is a rare variant of Ewing Sarcoma reported by van Haelst et al in 1975. Further, as described by Mahadevan P et al, ALES, show characteristic epithelial differential and strong cytokeratin expression. ALES are most common in the head and neck sites, however; recently, few cases have been reported in the abdominal cavity and thyroid gland as well. The current cases reported are one in the pancreatic tail and the other in the spine. The case of the 64yr old male in the pancreatic tail is only the **second case** of ***Adamantinoma-like Ewing Sarcoma Family of Tumors*** currently reported in literature, the first reported in 2023 by Wang Z et al [2].

These tumours share some morphological characteristics with their counterparts in the head and neck such as monotonous cytology, infiltrative growth pattern, palisade-like arrangement, and complex epithelial differentiation. These tumors harbor the t (11; 22) translocation and EWSR1-FL1 gene fusion, traditionally considered characteristic for Ewing sarcoma [4]. The immunohistochemical and molecular profile like diffuse membrane staining of CD99, significant nuclear expression of FLI1 and NKX2.2, with expression of epithelial markers including Pan CK, p40 are also shared with its counterpart. The first case reported in 2023 was in the pancreatic tail of a 43-yr-old male. The IHC studies of our case also showed similar picture as seen in this case. FISH for both EWS gene break and the EWSR1-FLI1 gene fusion were positive (Fig 16), and EWSR1-WT1 translocation was negative [2]. In 2019 Mahadevan P et al had reported a sinonasal case of ALES in an 18-yr old male. The IHC profile results were similar to what was seen in the current case. IHC was negative for actin, desmin, and WT-1. Molecular analysis revealed EWSR1 and FLI1 rearrangements and was positive for EWS-FLI-1 translocation. This report emphasized that a strong and diffuse CD99 positivity should prompt molecular testing for the presence of EWSR1 gene rearrangements.

Our second case in the lumbar spine of an 18yr old male also showed a similar immunohistochemical profile along with the expression of neuroendocrine markers which is well known in ES/PNET. In some other previous studies, ALES has been reported in few other locations like parotid gland, metatarsal bone etc. but the current two cases are at relatively rare locations like pancreatic tail and spine, thus making ALES in pancreatic tail, the second such case in history. As described by Marais et al in their case on metatarsal bone, there have been very few cases of ALES reported in the vertebrae or appendicular skeleton. This, along with overlapping clinical features as well as neuroimaging studies of the spine, may often present a diagnostic dilemma for the reporting pathologist [5, 6]. Hence, detailed immunohistochemical workup and molecular studies are advised for the confirmation of the diagnosis in these cases.

The diagnostic dilemma encountered while working up these cases were expression of epithelial markers and going down the tract of a carcinoma. Hence it is important to be alert about the diagnostic pitfalls and look at the morphology with the rare differentials in mind.

Differentiating carcinoma versus ALES is important as treatment strategies are different.

Dorand et al in their multicenter evaluation study on treatment strategies in ALES, emphasized a multidisciplinary approach defining the clinical characterization for guiding the treatment options and determining the prognosis [7].

Conclusion:

ALES is thus a rare and aggressive malignancy that is difficult to diagnose and treat. Given the scarce nature of ALES, and its rarity in the pancreatic tail and the spine, the documentation of such cases is vital for enhancing the medical understanding of this entity. The recognition of ALES in some uncommon locations adds a significant layer of complexity to diagnosing and managing these tumors. The diagnosis was made based on the morphological, immunohistochemical, and molecular findings. The prognosis for this disease is poor, and further research is needed to improve diagnosis and treatment. The case further highlights the need for thorough histopathological examination and the potential utility of multimodal diagnostic approaches in identifying such rare entities. Owing to its rarity, it is necessary to study all ALES cases from treatment perspective to understand the prognosis.

Ethical Approval:

As per international standards or university standards written ethical approval has been collected and preserved by the author(s).

Consent

Written patient Consent was signed as part of Test Requisition form (TRF)

Funding Sources

No source of funding.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

Figures

Case 1:

H& E Images

Fig 1: Tumour involving the spleen and pancreas

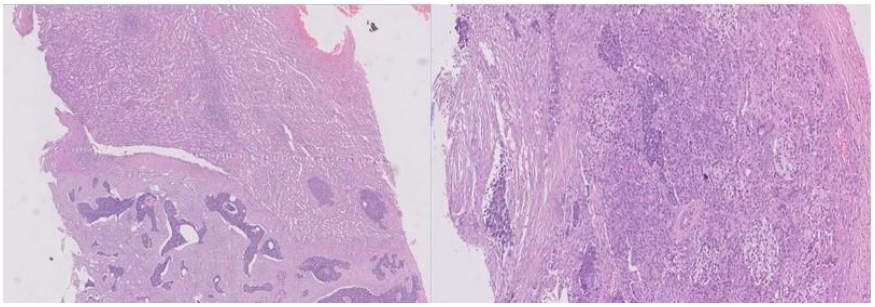
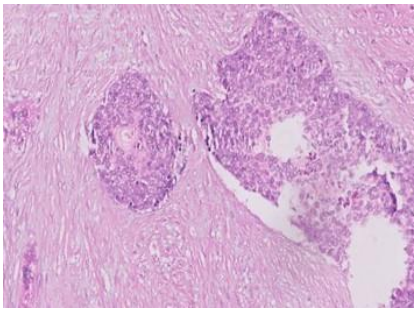


Fig 2: Tumour with central squamous differentiation



Positive IHC markers

Fig 3: *pan-CK*

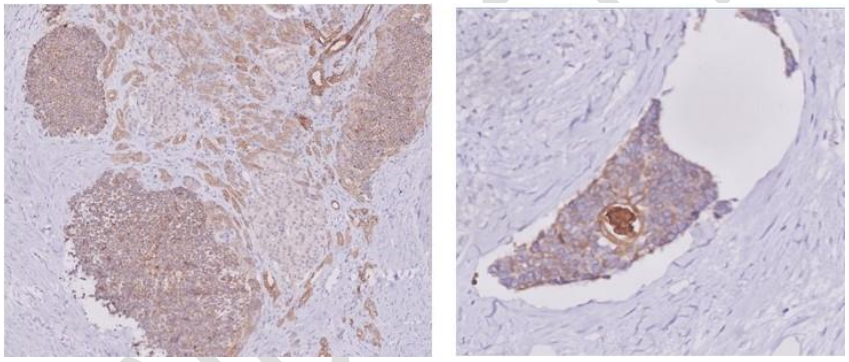


Fig 4: *p40*

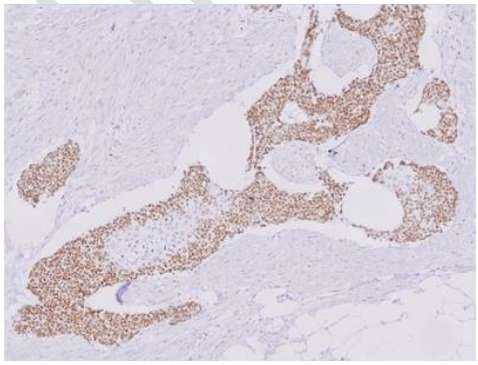


Fig 5: *Ki67*

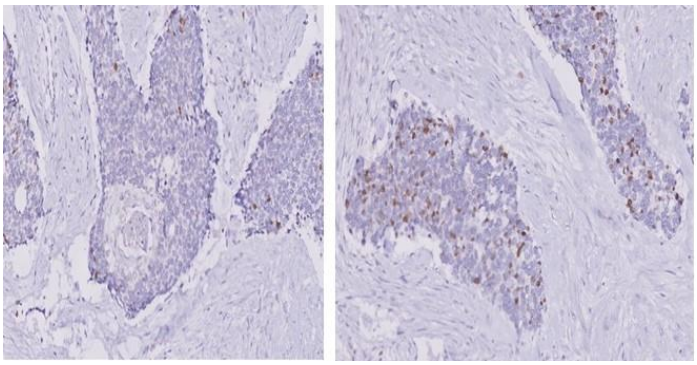


Fig 6: CD99

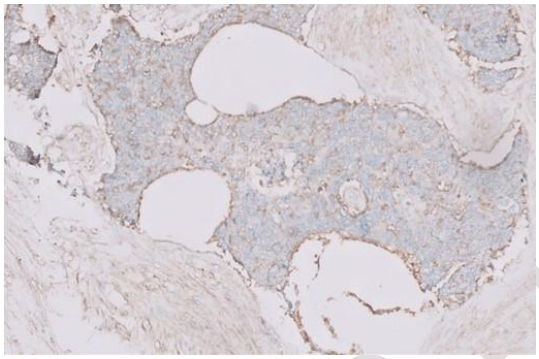
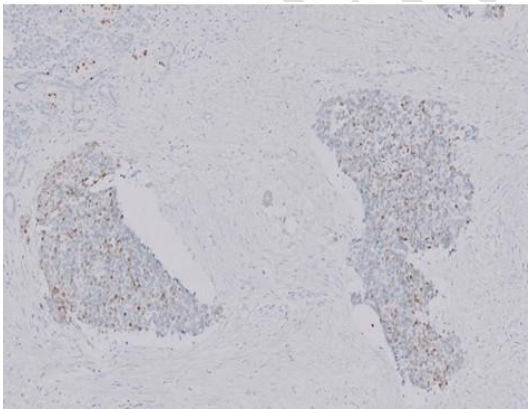


Fig 7: NKX2.2



Case 2:

Fig 8: H&E Image

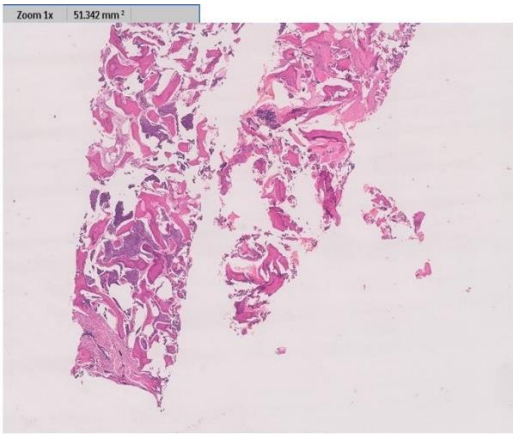


Fig 9: Round cell tumour involving the bone

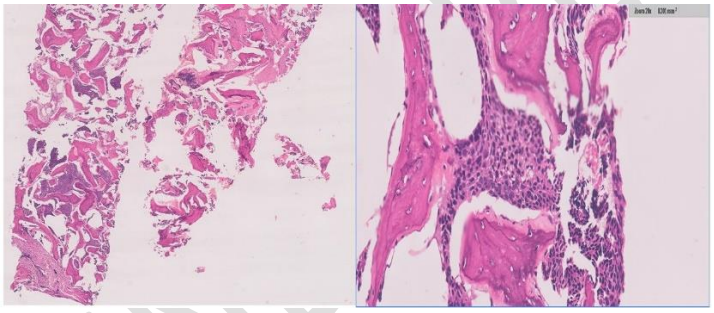
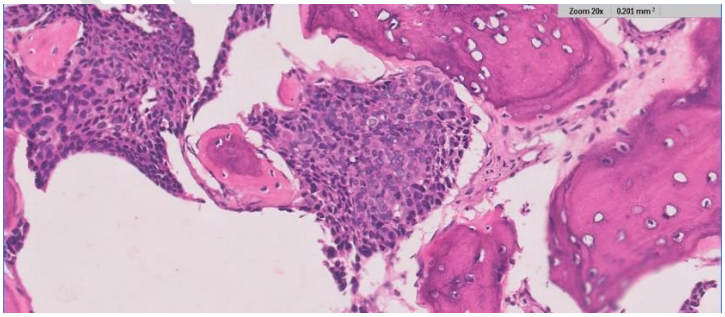


Fig 10: Medium power appearance of tumour within the bone



IHC positive markers

Fig 11: P40

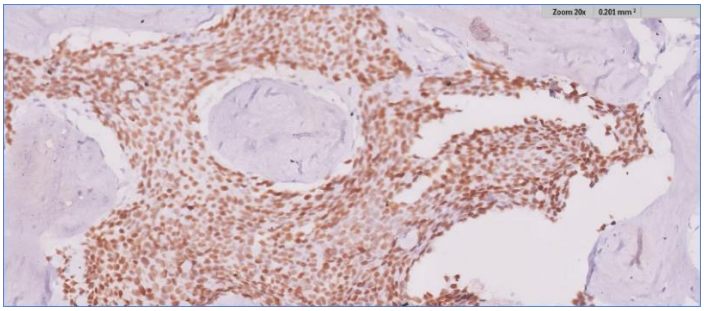


Fig 12: P63

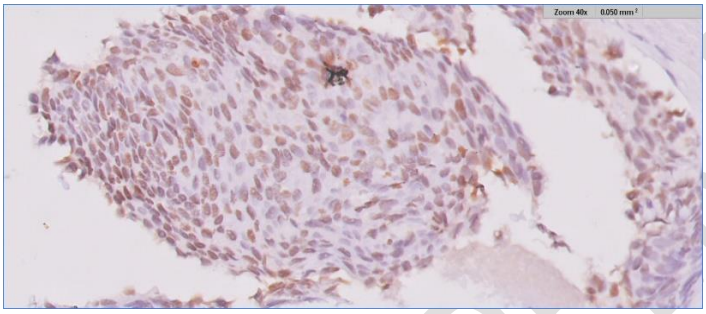


Fig 13: pan-CK

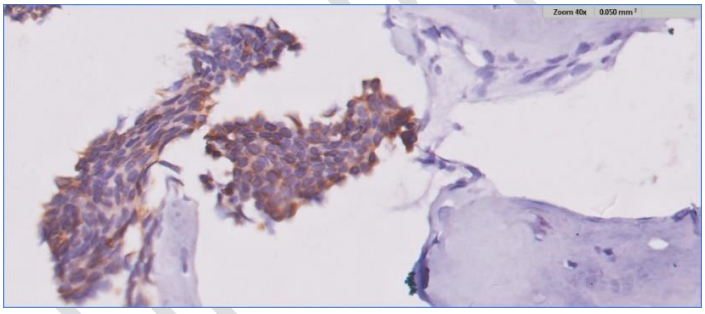


Fig 14: SYNAPTO

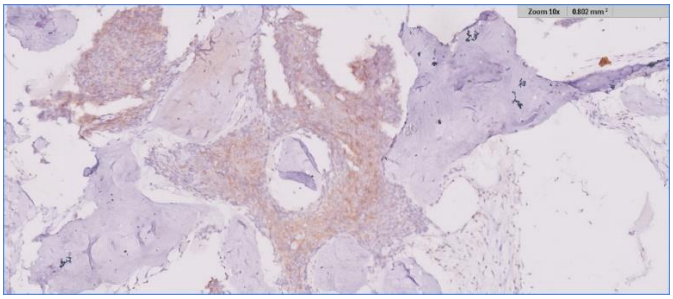


Fig 15: NKX2.2

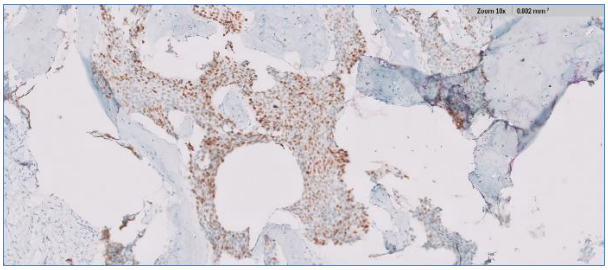
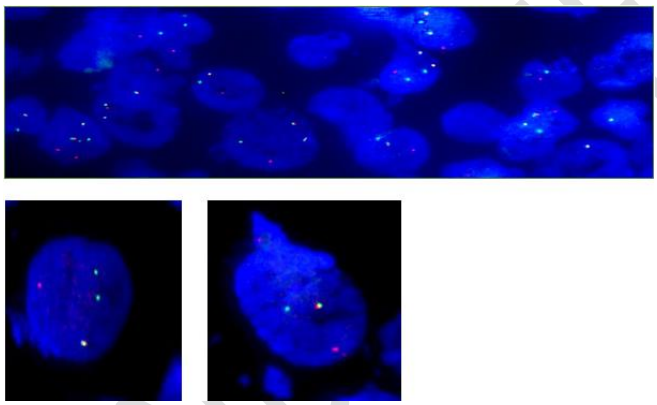


Fig 16: Interphase cells showing EWSR1 gene t(22q12) rearrangement positive status by FISH



Disclaimer (Artificial intelligence)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

References:

1. *Agaimy A, Hartmann A, Antonescu CR, Chiosea SI, El-Mofty SK, Geddert H, et al. SMARCB1 (INI-1)-deficient sinonasal carcinoma. The American Journal of Surgical Pathology [Internet]. 2017 Mar 14;41(4):458–71. Available from: https://doi.org/10.1097/pas.0000000000000797*
2. *Wang Z, Wen X, Zhang Y, Zhang X. Adamantinoma-like ewing sarcoma arising in the pancreatic tail: a case report of a rare entity and review of the literature. Diagnostic Pathology [Internet]. 2023 Jul 31;18(1). Available from: https://doi.org/10.1186/s13000-023-01374-0*
3. *Dorand RD, Wang DY, Keedy VL, Davis EJ. A multicenter evaluation of treatment patterns and outcomes for Adamantinoma-like Ewing sarcoma. Journal of Clinical Oncology [Internet]. 2022 Jun 1;40(16_suppl):e23500. Available from: https://doi.org/10.1200/jco.2022.40.16_suppl.e23500*
4. *Rooper LM, Bishop JA. Soft Tissue Special issue: Adamantinoma-Like Ewing Sarcoma of the Head and Neck: A Practical Review of a challenging emerging entity. Head and Neck Pathology [Internet]. 2020 Jan 16;14(1):59–69. Available from: https://doi.org/10.1007/s12105-019-01098-y*
5. *Wang Z, Zhang X, Zhang Y, Wen X. Adamantinoma-like ewing sarcoma arising in the abdominal cavity: A case report of a rare entity and review of the literature. Research Square (Research Square) [Internet]. 2023 May 31; Available from: https://doi.org/10.21203/rs.3.rs-2964419/v1*
6. *Marais YA, Saini A, Ferreira N, Reddy K, Zühlke A, Rossouw N, et al. Adamantinoma-like Ewing Sarcoma in a Metatarsal Bone After Chemotherapy Treated with an Osteocutaneous Fibular Transfer: A Case Report. Research Square (Research Square) [Internet]. 2020 Oct 26; Available from: https://doi.org/10.21203/rs.3.rs-96041/v1*
7. *Dorand RD, Wang DY, Keedy VL, Davis EJ. A multicenter evaluation of treatment patterns and outcomes for Adamantinoma-like Ewing sarcoma. Journal of Clinical Oncology [Internet]. 2022 Jun1;40 (16_suppl):e23500. Available from: https://doi.org/10.1200/jco.2022.40.16_suppl.e23500*