

Case report

CIC-rearranged sarcoma presenting with superior vena cava syndrome: case report

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Summary

CIC-rearranged sarcomas are rare mesenchymal neoplasms belonging to the family of undifferentiated small round cell sarcomas. This report details the case of a 45-year-old man presenting with symptoms of mediastinal compression, radiological diagnosis of a mediastinal mass and rapid evolution to full-blown superior vena cava syndrome. The emergency was successfully managed with a pharmacological approach. Formulation of a pathological diagnosis of CIC-rearranged sarcoma was initially supported by fluorescence in situ hybridisation findings and later validated by next-generation sequencing, which showed CIC-DUX4 gene fusion. A chemotherapy regimen was started with immediate benefits for the patient. The spectrum of pathological entities able to cause superior vena cava syndrome is wide, and recognition of rare causes is important to tailor the therapeutic approach to the specific disease. This is, to the best of our knowledge, the first report of CIC-rearranged sarcoma presenting with superior vena cava syndrome.

Key words: case report, CIC-rearranged, mediastinum, superior vena cava syndrome, sarcoma

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Introduction

CIC-rearranged sarcomas are high-grade, undifferentiated, mesenchymal neoplasms characterised by a spectrum of possible CIC gene rearrangements, the most common of which being CIC-DUX4 fusion resulting from either a t(4;19)(q35;q13) or a t(10;19)(q26;q13) translocation¹. CIC-rearranged sarcomas have only recently been recognised as distinct entities by the WHO classification of soft tissue tumours², previously being considered part of the Ewing sarcoma-like family. CIC-rearranged sarcomas are very rare, but precise epidemiological data are not available. They have been described in patients of almost any age, with a peak incidence around the fourth decade. The typical primary location is the deep soft tissues, with a minority arising in viscera or bones¹.

On microscopic examination, CIC-rearranged sarcomas share many features with other Ewing-like sarcomas, as they are usually characterised by a dense, often nodular proliferation of small, round, relatively monomorphic cells with scant cytoplasm that may appear clear¹. Neoplastic cells are immunoreactive for antibodies against WT1, ETV4 and CD99, with the latter immunostaining typically being more patchy than what is seen in Ewing sarcoma¹. Fluorescence in situ hybridisation

(FISH) and next-generation sequencing (NGS) are techniques able to detect the presence of CIC gene rearrangements, and are usually needed to render the correct diagnosis¹.

CIC-rearranged sarcomas have a dismal prognosis, most cases presenting with large masses (> 5 cm), sometimes with metastatic disease, usually involving lungs. 5-year overall survival is less than 50%, meaning that prognosis is poor compared with Ewing sarcoma, a fact that is at least partly accounted for by the lower responsiveness to chemotherapy¹.

Case report

We present the case of a 45-year-old man seeking medical attention for the recent onset of dry cough and exertional dyspnoea. The patient had no relevant clinical history and underwent CT-scan, which showed a 12 cm mass occupying the anterior compartment of the superior mediastinum and presence of multiple pulmonary lesions suggestive of metastatic disease. Further oncological work-up of the patient's disease was hindered by the sudden onset of symptoms of superior vena cava (SVC) syndrome, developing a few weeks after the initial radiological finding. The patient experienced neck oedema, distension of the neck veins and facial plethora; thus, he was admitted to the emergency department. Thoracic CT-scan was repeated, confirming the presence of the mediastinal mass and showing infiltration of the SVC above the azygos vein, with thrombotic phenomena extended to the left brachiocephalic trunk (Fig. 1). The radiologi-

cal differential diagnosis encompassed a wide range of pathological entities, including carcinomas, thymic neoplasms, lymphomas and dysgerminomas. The patient was initially managed with heparin and high-dose corticosteroids, leading to rapid relief of symptoms. Endovascular stenting was deemed unnecessary as the clinical picture appeared stable and the risk of complications was considered excessive. The patient underwent video-assisted thoracoscopy. Both wedge resection of a pulmonary lesion and biopsy of the mediastinal mass were performed. Histopathological examination of the lesional tissue showed a multinodular proliferation of small, round, monomorphic cells with clear cytoplasm (Fig. 2A). WT1 immunostaining was diffusely positive (Fig. 2B), while CD99 immunoreactivity was patchy (Fig. 2C). FISH (Fig. 3) allowed detection of CIC gene rearrangement, confirming the pathological suspicion of CIC-rearranged sarcoma. NGS was later performed on the case as well, for the purposes of further diagnostic validation and of accurate case description. An RNA-based panel (FusionPlex Sarcoma kit, Archer, USA) was used for the investigation of fusions in most genes known to be involved in soft tissue pathology. The results showed a CIC-DUX4 gene fusion, with breakpoints located in exon 20 of the CIC gene and exon 1 of the DUX4 gene (chromosome 4). No other anomalies were identified in the analysed gene panel.

Following the formulation of the diagnosis, a multi-agent chemotherapy regimen was instituted, with further improvement of the patient's symptoms.



Figure 1. Axial, contrast-enhanced, high resolution CT scan with mediastinal (A and B) and lung (C) window. There is an antero-superior mediastinal mass showing heterogeneous density and evidence of superior vena cava invasion with significant yet incomplete obstruction of the lumen. Multiple nodular lesions, suspicious for metastatic disease, affect the lungs bilaterally.

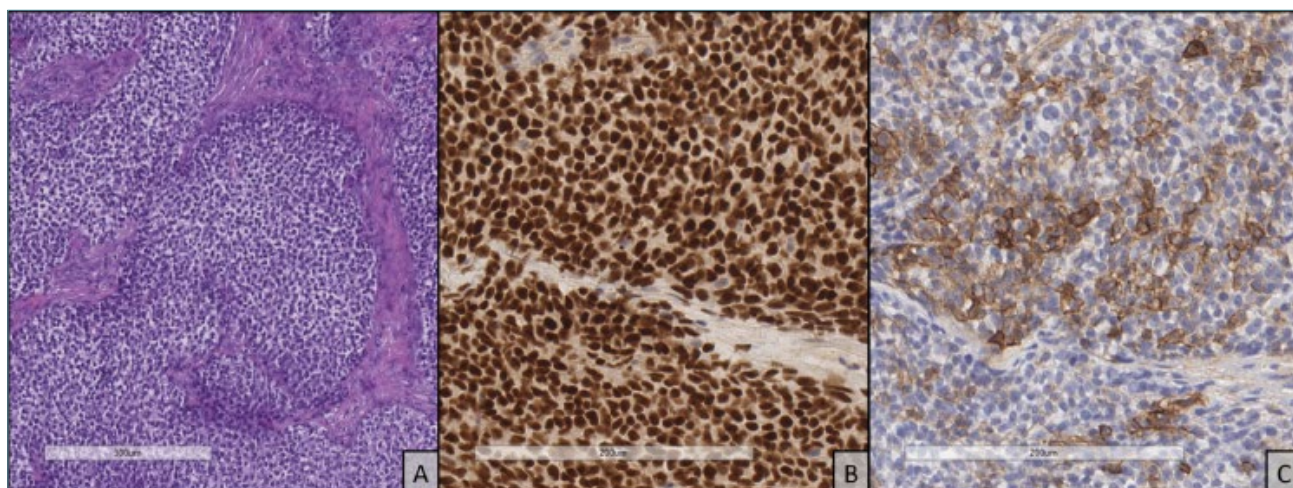


Figure 2. (A) The lesion is composed by nodules of small, round cells separated by fibrous septa. The cells are characterised by dense growth, minimal pleomorphism and clear cytoplasm (H&E; 10x). (B and C) Immunohistochemistry for WT1 (B), shows diffuse and intense positivity, while staining for CD99 (C) is patchy and of moderate intensity (immunohistochemistry; 20x).

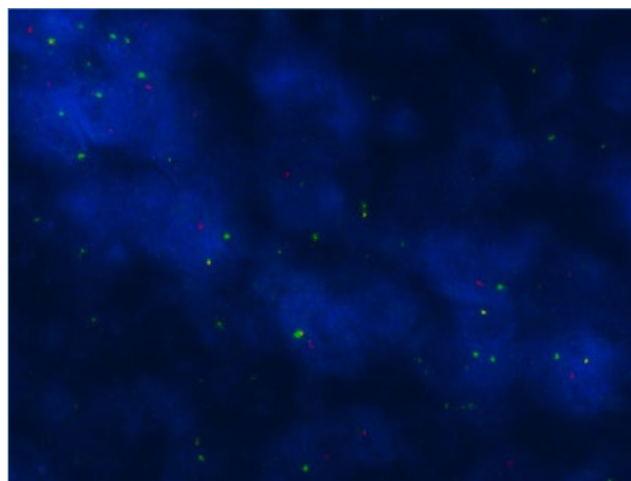


Figure 3. FISH with break-apart CIC probe, showing split red and green signals, demonstrating rearrangement of the CIC gene.

Discussion

SVC syndrome is estimated to occur in around 15000 patients per year in the US³. Currently, SVC syndrome is considered to be caused by malignancies in about 70% of cases, with the remaining portion being mostly device-related. Pathological definition of the cause of SVC syndrome is crucial to inform therapeutic decisions, with radiotherapy, chemotherapy, surgery, glucocorticoids and combined approaches being most beneficial in different settings^{3,4}. Among the malignant

etiologies of SVC syndrome, non-small cell lung cancer represents the main culprit (50% of cases), small cell lung cancer accounts for 25% of cases, lymphomas (B or T) for 10% and few other pathological entities account for the remaining cases. Even among this heterogeneous last category, sarcomas are considered to be rarer agents than other neoplasms such as metastatic carcinoma, germ cell cancer, thymoma and mesothelioma³. Mediastinal sarcomas represent around 1% of all soft tissue sarcomas⁵ and probably less than 5% of all mediastinal neoplasms⁽⁶⁾. Determination of the precise epidemiology of the many different sarcoma subtypes that can arise in the mediastinum has been hindered by the rarity of these entities, the differences among the various mediastinal compartments and the evolution of the pathological classification of soft tissue neoplasms, which has progressively made retrospective data obsolete⁵. Even after these considerations, there are some sarcoma subtypes that emerge from the literature as relatively prevalent in the mediastinum, including liposarcoma, synovial sarcoma, malignant peripheral nerve sheath tumour, leiomyosarcoma and small round blue cell sarcomas⁵. Data from these cohorts mostly predate the introduction of CIC-rearranged sarcoma as a distinct pathological entity and are likely to consider such cases as small round blue cell sarcomas. We now know that CIC-rearranged sarcomas are exceptionally rare not only among sarcomas in general, but even among small round blue cell sarcomas, of which they only represent 1%, with the vast majority being Ewing sarcomas (> 95%)⁷.

Searching the literature specifically for SVC syndrome caused by sarcomas only yields case reports, mostly dealing with vascular neoplasms. In 2015, Madabhavi et al. described a case of primary mediastinal synovial sarcoma causing SVC syndrome⁸, a report with some similarities to the one we presented. In fact, synovial sarcoma is much more common than CIC-rearranged sarcoma and has a much shorter list of histopathological differential diagnoses. CIC-rearranged sarcomas indeed have many histological mimics of impressively different origins, such as all Ewing-like sarcomas (mostly Ewing sarcoma and BCOR-rearranged sarcoma), mesenchymal chondrosarcoma, poorly differentiated synovial sarcoma, desmoplastic small round cell tumour, small cell osteosarcoma, small cell carcinoma, Merkel cell carcinoma, lymphoblastic lymphoma and neuroblastoma. To formulate a histopathological diagnosis of CIC-rearranged sarcoma, especially in an unusual and time-sensitive setting such as the one of this report, one has to be familiar with the typical morphology of this neoplasm (small round cells), its relatively specific immunophenotype (WT1+, CD99+ patchy) and its characteristic genetic signature (CIC gene rearrangements), detectable by FISH or gene sequencing¹.

Conclusion

To our knowledge, this is the first described case of mediastinal CIC-rearranged sarcoma presenting with SVC syndrome.

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Conflicts of Interest

The authors have no conflict of interest relevant to the present work.

Ethical Consideration

This is a case report, everything concerning it complied with the principles outlined in the declaration of Helsinki.

Author Contributions

AA: investigation, writing – original Draft, writing – review and editing, visualization, project administration; GM: investigation, project administration; FDD: investigation; BC: writing – review and editing, investigation; RC: conceptualization, supervision; SA: conceptualization, supervision.

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