CASE REPORT

Invasive thymoma presenting as classic superior vena cava syndrome: a case of venous spread metastasis

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SUMMARY

The approach to an intrinsic cause of superior vena cava syndrome (SVCS) is usually difficult but rewarding. We report a case of a middle-aged man who presented with progressive oedema of the upper half of the body, dyspnoea, cough and weight loss for a 1-year duration. He was a non-smoker without prior hospitalisation. Chest radiography showed right-sided pleural effusion with an apparent normal superior mediastinum. Contrast-enhanced CT of the chest revealed a right atrial mass extending and completely obliterating to superior vena cava. The differentials were tuberculosis, invasive fungal granuloma, sarcoidosis, primary vasculitis, chronic venous thrombosis, cardiac sarcoma/lymphoma and metastatic thyroid tumour or thymoma. He underwent transvenous (femoral approach) biopsy of the mass and then cardiothoracic surgery after haemodynamic instability. Pathology showed invasive thymoma type B3. This case highlights the approach to an intrinsic cause of SVCS, a complication of the transvenous approach, and importantly a noble finding of venous spread metastasis.

BACKGROUND

Superior vena cava syndrome (SVCS) occurs when there is obstruction of blood flow in the path from great veins draining into the superior vena cava (SVC). During the past century, the major focus on etiopathogenesis of the syndrome has shifted from the infection to malignancy to intravascular device-related complications. Yet malignancy accounts for up to 85% of the aetiology and can present as SVCS in up to 60% of cases.¹ There are three major pathogenic mechanisms: (1) compromised vessel anatomy, for example, mediastinal mass causing extrinsic compression; (2) compromised vessel wall integrity, for example, vasculitis; (3) compromised venous flow, for example, intravascular thrombus/mass causing intrinsic compression.² Imaging can easily differentiate between these types; however, the aetiological approach is cumbersome because of the risk attached to different procedures.

Thymoma, a tumour of thymic epithelial cells, is commonly seen in the anterior mediastinum in 90% of cases and rarely in the neck or other mediastinum sites.³ It presents uncommonly as SVCS (only 2% of all malignant aetiology).⁴ The mechanism is often extrinsic compression to SVC. Rarely, intrinsic compression is seen through venous spread, that is, permeation of tumour cells through thymic veins, brachiocephalic veins, SVC and right

atrium (RA), exactly similar to renal cell carcinoma migrating through renal veins/inferior vena cava.⁵ The reason for this typical character is not known; maybe it is tumour biology. There are only <10 case reports of this type of intraluminal spread of invasive thymoma/thymic carcinoma.⁶

We report a rare presentation of invasive thymoma as an intrinsic cause of SVCS where an insight into the pathogenesis of the tumour spread is found.

CASE PRESENTATION

A 55-year-old man presented with a 1-year history of painless progressive symmetrical swelling of the upper limbs, chest, head and neck. It was associated with dry cough and progressive dyspnoea. He had anorexia, fatigue and unintentional weight loss (~7 kg) over 2 months. There was no associated fever, throat/chest pain or syncope. Initially, he received diuretics for symptomatic relief and his routine investigations including chest radiograph were normal. He had primary hypothyroidism for 7 years and was on levothyroxine (50 µg) supplementation. He denied any substance abuse, prior surgery or hospitalisation.

On examination, he had tachypnoea, but other vitals were normal. He had oedema over head, neck, upper chest, and both upper limbs without visible dilated veins. Chest examination demonstrated reduced respiratory excursions, dullness on percussion and decreased breath sounds at the base of the right hemithorax. Jugular venous pressure could not be measured due to an oedematous neck. Other cardiac examination was normal. The liver was tender and palpable, 2 cm below the costal margin. Hence, classic SVCS was diagnosed but without having any critical issues, viz, substantial haemodynamic compromise, laryngeal oedema or cerebral oedema.

Since SVCS was an oncological emergency, urgent laboratory workup was performed that revealed nothing except marked transaminitis (>10 times the upper reference limit), suggesting a possibility of ischaemic hepatitis due to right-sided heart failure. Chest radiograph showed moderate right-sided pleural effusion with a normal superior mediastinal contour (figure 1A). An electrocardiogram revealed normal sinus rhythm. Transthoracic two-dimensional echocardiography showed a RA intracavitary mass extending up to the SVC. Contrast CT of the chest reconfirmed an RA/SVC intraluminal mass with heterogeneous enhancement and

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Figure 1 Basic imaging of an intrinsic cause of superior vena cava syndrome. (A) Chest radiograph showed right-sided moderate pleural effusion with the mediastinum slightly pushed towards the left side. Upper/superior mediastinum was appearing normal. (B) Coronal section of contrast-enhanced CT of the chest showed a large intravascular mass in the right atrium and superior vena cava (→) and similar nature mass in the prevascular area (bend ↔), without evidence of any calcification or fat density, moderate right-sided pleural effusion (**) and mild pericardial effusion (*) being seen. Note was also made of few venous collaterals (←→). Axial section (C) showed both an intravascular mass and prevascular mass at arch of aorta level without having continuity. Axial section (D) showed chronically thrombosed bilateral brachiocephalic veins with luminal obliteration (→) and adjacent prevascular mass (bend →).

another similar nature lesion in the prevascular space (figure 1B–D). Diagnosis of SVCS due to an intravascular/intracardiac mass was made, an aetiological approach started and symptomatic treatment continued.

DIFFERENTIAL DIAGNOSIS

Considering the epidemiology, chronic symptomatology, pathology affecting the pleura and mediastinum and image characteristics, few differentials were considered. These were tuberculosis, invasive fungal granuloma, sarcoidosis, primary vasculitis, chronic thrombus in a hypercoagulable patient, cardiac sarcoma/lymphoma and metastatic thyroid tumour or invasive thymoma.

INVESTIGATIONS

Cardiovascular tuberculosis was less likely due to transudate pleural effusion and lack of necrotic mediastinal lymph nodes. Other laboratory workup for tuberculosis, fungal infection and chronic thrombus was negative (erythrocyte sedimentation rate, Mantoux test, serum galactomannan assay, viral markers and tests for thrombophilia). Furthermore, invasive fungal granuloma and sarcoidosis were also less likely due to lack of an aggressive lesion involving the mediastinum, heart and pulmonary veins and of mediastinal lymphadenopathy (non-necrotic) and granuloma involving the myocardium. The most common intracavitary cardiac mass lesion is a thrombus due to either a hypercoagulable state or intravascular device and their characteristic property is non-enhancing nature.⁷ However, the lesion in question was heterogeneously enhancing. Primary tumours involving the RA are mainly angiosarcoma and, rarely, myxoma and lymphoma; however, they are aggressive, diffusely infiltrating across various tissue planes with transvalvular and aortic root involvement, and having large areas of necrosis and heterogeneity that were not evident in our case.⁸ Secondary tumours metastasising to RA/SVC are usually from lung, breast, skin

(melanoma), thyroid and thymus. These tumours usually have extrinsic compression of SVC, easily recognised by imaging. Venous spread of the tumour causing intrinsic SVC compression is a recently known fact, studied by few case reports of thyroid and thymic tumours. Thyroid examination was normal in the study case. Tumour markers (α -fetoprotein, β -human chorionic gonadotropin, prostate-specific antigen and carcinoembryonic antigen) were negative or in the normal range. Immunoglobulin levels were normal. The thyrotropin (thyroid-stimulating hormone) level was elevated (19 IU/L) and hence his thyroxine supplementation was increased (75 μ g).

For more characterisation of the mass, gadolinium contrast MRI of the mediastinum was performed that showed the cardiac mass with conglomeration (nodular areas of contrast enhancement) and maintaining integrity of the RA wall, suggesting an intraluminal growing mass. There was another prevascular mass with the same characteristics; however, they were seemed to be in continuity along the venous channels with thrombus in bilateral brachiocephalic veins (figure 2A, B). Multiple collaterals were seen, especially for the SVC, azygous vein and thoracic duct. Positron emission tomography CT revealed a mild uptake of contrast in both masses (figure 2C, D).

At this point of time, differentials were reduced to either metastatic tumour (more likely) or disseminated granulomatous lesions. To make tissue diagnosis, he underwent a transvenous (femoral approach) biopsy of the RA/SVC mass after risk stratification because of an issue of inadequate sampling in the small prevascular mass. The procedure was successful but his haemodynamic status deteriorated on postoperative day-3 and he was taken up for urgent debulking cardiothoracic surgery. Here, stenting could have been performed, but for both diagnostic and therapeutic purposes open surgery was performed. Intraoperatively, the mass was not arising from any wall of RA; rather, it originated from the SVC. It was completely removed from the RA and as much as possible from the SVC. Grossly, it

Figure 2 Advanced imaging of an intrinsic cause of superior vena cava syndrome. MRI coronal image (A) showing a large right atrium intracavitary mass extending into the SVC (→), a similar nature mass in the prevascular area (bend ↔), and a thrombus of brachiocephalic vessels. Note was also made of continuity of two masses along the venous drainage. An adjacent MR venogram showing bilateral brachiocephalic veins obliteration (↔) with evidence of multiple venous collaterals. (B) An early postcontrast T1-weighted four-chamber image showing heterogeneous enhancement of the RA mass (→). An adjacent late gadolinium enhanced four-chamber image also showed heterogeneous enhancement of the mass with evidence of conglomeration (→). (C and D) Positron emission tomography (PET) CT image showed mild uptake of the RA/SVC mass lesion (→). RA, right atrium; SVC, superior vena cava.

measured 11×6.5×4.5 cm in size showing a congested and intact capsule. Histopathological examination revealed a lobulated appearance of the tumour separated by thick fibrous and hyalinised septa. These lobules were predominantly composed of epithelial looking cells arranged in solid sheets with sparsely dispersed lymphocytes. Individual cells were round to polygonal in appearance with a moderate amount of cytoplasm, minimal nuclear pleomorphism, atypia and few mitotic figures (figure 3A, B). Immunohistochemical analysis was positive for pan-cytokeratin (CK 19), synaptophysin, epithelial membrane antigen, CD3, CD1a and TdT, and negative for TTF-1 and

chromogranin (figure 3C, D). The proliferative index (Ki-67 index) of the tumour was approximately around 40–45%. The diagnosis was consistent with type B3 thymoma (well differentiated thymic carcinoma) with modified Masaoka stage III, spreading through thymic veins, brachiocephalic veins, SVC and RA.

TREATMENT

The patient was started on adjuvant radiotherapy immediately after debulking surgery as soon as report came to be invasive thymoma. This brief session of radiotherapy was followed by

Figure 3 Immunohistopathology of an intravascular/intracardiac mass. Microscopy on H&E staining showing (A) ×10, a lobulated tumour separated by thick hyalinised fibrous septa; (B) ×20, predominantly of epithelial cells with very sparse interspersed lymphocytes. Immunohistochemistry staining revealed (C) ×40, epithelial cells of strong membranous positivity for cytokeratin (CK) and (D) ×40, interspersed lymphocytes positivity for TdT.

regular adjuvant chemotherapy (CAP regimen as discussed below). He completed a total of five cycles of chemotherapy. Meanwhile, workup for paraneoplastic syndrome (ie, myasthenia gravis, hypogammaglobinaemia and pure red cell aplasia) associated with thymoma was negative.

OUTCOME AND FOLLOW-UP

He is doing well now. The last follow-up images did not show any mediastinum pathology except a subcentimetre size of pre-vascular mass. The plan is to give him two more cycles of chemotherapy and follow-up regularly every 6 months for a few years, followed by chest imaging annually (low dose CT).

DISCUSSION

SVC is very prone to compression/obstruction due to its thin wall and being in a non-distensible space in the mediastinum that leads to SVCS.⁹ Swelling and/or dilated veins over the upper torso, dyspnoea (sometime orthopnoea) and cough are the most common symptoms of the syndrome. Careful examination can rule out differentials like congestive heart failure, pericardial disease or Cushing's syndrome.¹ After diagnosing the syndrome, proper assessment of critical issues, for example, substantial haemodynamic compromise, laryngeal oedema or cerebral oedema should be performed. This is the first step in approaching the case. Their presence leads to early intervention in the form of urgent stenting, thrombolysis or surgery. There are no professional guidelines addressing the management of the syndrome except the treatment advised by the American College of Chest Physicians and the National Comprehensive Cancer Network for lung cancer.⁴ Few studies reported stenting as a first-line intervention.¹⁰ Surgery is preferred in a known case of resectable tumour (eg, thymoma, residual germ cell mass). Previously used emergency radiotherapy is being used rarely due to interference with the diagnosis and delayed results.¹ Sometimes, other manoeuvres (oxygen supplementation, elevating the head end of the bed, diuretics and corticosteroids) are advised though not much is known about their efficacy. Nevertheless, the primary goal in SVCS management is alleviation of symptoms and treatment of the underlying disease.

The workup for aetiological diagnosis, including tissue biopsy as the second step in approaching a case of SVCS, should be performed as early as possible because the presence of the syndrome does not change the prognosis in the same tumour type and disease stage; rather, treatment depends on the aetiology.⁴

Imaging is essential for confirming the diagnosis, characterising the pathology, grading the severity, facilitating the intervention and deciding whether obstruction is resectable or not. Chest radiography may show superior mediastinal widening and hilar prominences, seen in 33–100% of cases.¹¹ However, in the absence of extrinsic compression, the findings may not be apparent. CT or MRI with contrast is the primary modality of choice. MRI study of the mediastinum has few advantages over CT, including the ability to image in many planes of view and directly visualising blood flow without use of iodinated contrast material; however, cost and patient non-compliance are high.⁹

Less invasive tests like sputum cytology, pleural fluid cytology and biopsy of peripheral enlarged lymph nodes like supraclavicular, if these are present, are advocated and might be diagnostic in up to two-thirds of cases.¹² Pleural effusions of SVCS are often moderate in quantity and of exudative type. The pathophysiology remains multifactorial: (1) thoracic duct outflow obstruction; (2) malignant effusion (cytology is positive in 53% of cases); (3) use of diuretics may convert transudate to apparently exudative, however, advanced investigations like serum-

pleural albumin gradient and Pro-BNP in pleural fluid may determine true nature of fluid; and (4) small pulmonary embolism.¹³ Sometimes, use of diuretics may convert transudate to apparently exudative, hence, precautions should be taken to rule out false positive cases by doing advanced investigations like serum pleural albumin gradient and Pro-BNP in pleural fluid. Our case had transudate, probably due to the left heart dysfunction by decreased preload after near complete obliteration of RA or part of uncontrolled hypothyroidism.

If everything fails, more invasive procedures starting from image-guided biopsy to open surgical biopsy are needed to reach a tissue diagnosis. All depends on the location of the mass causing the syndrome and expertise of the concerned physician because of a lack of guidelines. For an intrinsic cause of SVCS, open surgery is needed many a time. There are few case reports showing success for intraluminal biopsy through a transvenous approach (femoral/basilic); however, the chances of life-threatening bleeding and dissemination of pathology are high.¹⁴ Our case exemplifies the possibility of dissemination causing complete obstruction of inward flow of heart and haemodynamic instability and ultimately landed in open surgery.

After taking care of critical issues as discussed above and identifying the aetiology causing SVCS, further management depends on the primary cause of the syndrome, which is the third step in approaching the case. Here, it was invasive thymoma.

There are no randomised clinical trials that provide definitive guidance for the management of invasive thymoma. Guidelines from the National Comprehensive Cancer Network and by the Cancer Care Ontario programme are usually followed.^{15 16} The initial treatment depends on the clinical assessment of resectability. If completely resection is possible, surgery is advocated at first. Open surgical approach via a median sternotomy is the current standard of care. A minimally invasive (thorascopic/robotic) approach may be advised only for specialised centres. Postoperative pathology finding helps in the staging and determines about indication of postoperative radiotherapy. If complete resection is not possible, neoadjuvant chemotherapy or chemoradiotherapy is used prior to surgery after confirmed needle biopsy report to improve the likelihood of a complete surgical resection. Often, owing to lack of a biopsy report like in our case, maximum debulking followed by postoperative radiotherapy is the standard of care.¹⁷ Furthermore, in case of venous spread metastasis of the tumour, based on available case reports, radical surgery is preferred over induction therapy to save time and avoid tumour embolisation.¹⁸ Among many types of chemotherapy regimens, CAP regimen: cisplatin (50 mg/m² intravenously day 1), doxorubicin (50 mg/m² intravenously day 1) and cyclophosphamide (500 mg/m² intravenously day 1), repeated every 3 weeks, is universally used. Thymomas are usually slow-growing tumours, and the prognosis depends on the stage of disease and the complete resectability of the tumour. The Masaoka staging system is widely used to stage it and has correlated well with survival.¹⁹

There are few case reports (<10) of venous spread or intraluminal growth of invasive thymoma/carcinoma presenting as an intracardiac mass or SVCS. It has been found in a postoperative tissue sample that there is presence of tumour cells inside the veins from the thymus, extending upto RA in the venous channel.⁶ In contrast, intracardiac thymoma has been reported in many case reports which also include direct invasion of the atrial wall (extrinsic compression).²⁰ Our case was having venous spread without invading the atrial wall. Imaging and pathology confirmed the pathway of spread.

Learning points

- ▶ A multidisciplinary approach should be the standard of care for patients with superior vena cava syndrome (SVCS); however, stepwise management is of paramount importance.
- ▶ SVCS rarely requires emergency intervention (stenting, surgery or thrombolysis); however, interventions should be guided by the objective of not delaying biopsy.
- ▶ Once imaging confirms the intrinsic cause as mass, not thrombus/granuloma, open vascular surgery may be the only possible method for diagnosis and therapy.
- ▶ Intraluminal biopsy through a transvenous approach is having a dread complication of dissemination.
- ▶ Invasive thymoma, although very rare, can present as an intravascular/intracardiac mass by permeating through venous drainage leading to SVCS.

Contributors PKP developed the concept, searched literature, analysed and drafted the work, NW had analysed and critically revised the work. SK had performed radiological analysis, given their data, and drafted the work. SA had collected pathological data and drafted the work. All authors read and approved the final manuscript.

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