CASE REPORT

Mediastinal seminoma presenting with superior vena cava syndrome

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SUMMARY

We present a rare cause of superior vena cava syndrome (SVC) in a previously healthy male aged 31 years. Malignancy was suspected due to unintentional weight loss and childhood exposure to radioactive fallout from a nuclear facility accident. A very large anterior mediastinal mass was identified and demonstrated to be an extragonadal seminoma. Extragonadal germ cell tumours are rare tumours with a high potential for cardiovascular, pulmonary and vascular sequelae. Studies have documented an increased risk of developing seminoma in patients with radioactive exposure. Chemotherapy was initiated, during which the patient experienced progressive and new symptoms, found to be due to extensive thromboembolic disease, which responded well to anticoagulation. Seventy-two months after completing chemotherapy, without need for surgical management, he remains free of the disease.

BACKGROUND

Germ cell tumours most often arise from the gonads and metastasize; however, rare cases are primary extragonadal, accounting for 5.7% of all germ cell tumours in males.¹ The most common extragonadal site is the mediastinum.¹ While the origin of primary extragonadal germ cell tumours is still debated, the most accepted theory states they emerge from misplaced primordial germ cells that are retained in the extragonadal site.² Extragonadal germ cell tumours constitute 15% of primary anterior mediastinal tumours, and are significantly more common in males.³ Among these malignant tumours, 40% are seminomas.⁴ Kashcheev *et al* identified over 4000 solid tumours associated with the Chernobyl accident exposure in 1986, with a median exposure of 0.102 Gy.⁵ A Balkan study identified a 2.8-fold higher incidence of seminomas in Chernobyl accident survivors and soldiers exposed to uranium radiation during the Croatian War of Independence (1991–1995).⁶

CASE PRESENTATION

A previously healthy male aged 31 years with a prior history of vasovagal syncope was seen for further evaluation of progressive symptoms. He reported 2–3 years of worsening fatigue and a sensation of facial congestion for 12–18 months, including retro-ocular pressure when bending down or swimming. His wife and others noticed a dark red colouration of the scalp and face and neck vein distension when he bent down. He reported

feeling lightheaded during these episodes, but had no syncopal events. During autonomic testing, a documented blood pressure and heart rate decrease during vasovagal manoeuvres were appreciated and he had an inducible syncopal event from which he quickly recovered. The MRI and magnetic resonance angiogram of the patient's head and neck were unremarkable.

Over the few months, he had worsening facial and neck redness and fullness, such that he was symptomatic when lifting heavy objects, lying prone or supine or swimming. His degree of fatigue and exercise tolerance worsened despite prior high level of physical activity. He had no chest pain or pressure, syncope/near syncope or dyspnoea during any episodes, but reported upper back and chest discomfort. The patient's wife reported a noticeable unintentional weight loss of at least 15 pounds and she reported that the patient's face was very puffy in the morning, taking at least 3 hours to resolve. No peripheral oedema was noted by the patient or his wife but he reported intermittent bilateral upper extremity tingling. The patient denied any other symptoms and specifically had no fevers, night sweats, pain, dyspnoea or voice changes. Social history was notable for exposure to radioactive fallout from the Chernobyl disaster during his childhood in Belarus. He has never used tobacco or illicit drugs and drinks minimal alcohol.

INVESTIGATIONS

Normal laboratory results included liver and renal function, serum and urine protein electrophoresis, connective tissue and vasculitis studies, vitamin B12 (measured as methylmalonic acid), folate and vitamin D levels. He had a mild microcytic anaemia with normal iron studies. Autonomic studies repeated at our institution demonstrated a tendency to orthostasis and a possible mild autonomic neuropathy. Exercise ECG was unremarkable except for poor exercise capacity. A CT scan of the chest, abdomen and pelvis demonstrated an anterior mediastinal mass measuring 9.8 cmx6.7 cm causing SVC obstruction with collateral blood vessel development and compression of the pulmonary artery branch to the upper lobe of the right lung (figure 1). No adenopathy was identified. The CT-guided biopsy demonstrated a germ cell tumour favouring a seminoma. MRI of the head and the testicular ultrasound were normal. Serum α -fetoprotein was normal and β -human chorionic gonadotropin (β -HCG) was only mildly elevated at 3.5 IU/L (normal <2.0).

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Figure 1 CT chest January 2010 prior to initiation of chemotherapy showing large mediastinal mass.

DIFFERENTIAL DIAGNOSIS

On examination, he was thin (body mass index 20 kg/m^2) and vital signs were normal. Mental status was normal. Plethora with head and neck vein distension was observed when he bent far forward. Prominent superficial chest veins and nailbed cyanosis were also observed. His clinical presentation was concerning for SVC syndrome and differential diagnosis considerations included malignancy, structural heart disease, thromboembolic disease, vasculitis and connective tissue disease (eg, Behçet's disease or Marfan's syndrome).

TREATMENT

Thoracic surgery and medical oncology agreed the tumour was an extragonadal seminoma and chemotherapy with 3–4 cycles of bleomycin, etoposide and a platinum agent was recommended. A follow-up CT scan after the first cycle demonstrated significant tumour response with concomitant normalisation of his β -HCG, but persistent SVC syndrome. He was referred to vascular medicine. Given his haemodynamic stability and good collateralisation, a watchful-waiting approach was taken. After the second cycle, despite further reduction in tumour size, SVC syndrome symptoms persisted with new-onset left arm swelling and pain, and worsening facial and eyelid swelling. Persistent SVC compression was observed on imaging. Upper extremity duplex Doppler ultrasound demonstrated acute to subacute occlusive deep vein thrombosis through the left internal jugular, innominate, subclavian and axillary veins. Occlusive superficial thrombosis was seen through the entire left basilic vein and non-occlusive superficial venous thrombosis was seen within the right basilic vein at the level of the distal humerus (figure 2). A venogram demonstrated a very hard occlusion of the SVC that did not yield to vigorous probing with a guidewire. Low molecular weight heparin was initiated. Interventional radiology and vascular surgery were involved to consider recanalisation; it was determined this would not be successful and anticoagulation was continued. The patient responded well with decreasing left upper extremity pain and swelling. He was able to discontinue anticoagulation after 6 months of therapy with resolution of facial and left arm swelling. He had a pathologic complete response to chemotherapy, completing three cycles of cisplatin, etoposide and bleomycin (figure 3). Part of a fourth cycle of cisplatin and etoposide (3 days) without the bleomycin was completed. Due to his excellent response and intolerance of side effects, he elected not to receive further chemotherapy.

Upper Extremity Veins

Figure 2 Schematic representation of thromboembolism. LT, left; RT, right.

OUTCOME AND FOLLOW-UP

Seventy-two months after chemotherapy, the patient continues to have no evidence of disease recurrence and no evidence of recurrent thromboembolism.

DISCUSSION

Our patient presented with an extragonadal seminoma of the anterior mediastinum. Seminomas are most often diagnosed in patients aged 30–40 years, presenting with dyspnoea, chest pain, cough, fever, weight loss, SVC syndrome and fatigue.⁴

SVC syndrome, resulting from the obstruction of the SVC, is generally not life threatening itself.⁷ The SVC is susceptible to obstruction due to its thin walls and close proximity to lymph nodes that may cause external compression with enlargement. Symptoms and signs include dyspnoea, oedema of the face, arm(s) and neck, cough, changes in vision and hearing, fatigue, jugular vein distension and pleural effusion, all of which have onset of variable duration, and may be exacerbated by changes in position.⁷ A study conducted by Holbert and Libshitz⁸ demonstrated that 20% ($n=45$) of male subjects diagnosed with primary mediastinal germ cell tumours presented with this condition, consistent with the findings of previous smaller studies. While most cases are due to malignancy, SVC syndrome associated with

Figure 3 CT chest April 2010 after three cycles of chemotherapy showing significantly reduced mediastinal mass.

mediastinal masses is found in substantially younger patients with an average age of 27 years, as compared with the overall SVC syndrome presentation average of 55 years, most commonly associated with lung cancer.⁸ A previous case report highlighted presentation of a seminoma with bronchial involvement and SVC syndrome in a man aged 45 years.⁹ Other than mediastinal germ cell tumours, Hodgkin's disease is the most likely diagnosis for this population of young men; however, SVC syndrome in patients with this disease is rare.¹⁰ These data contribute to the conclusion that while extragonadal germ cell tumours of the mediastinum are rare, they should be included in the differential diagnosis of patients exhibiting SVC syndrome, particularly young men.⁸

Mediastinal tumours of this nature are most often identified by CT imaging demonstrating a bulky, lobulated, homogeneous mass. Metastases to the lymph nodes, lungs, bone or liver are common at presentation, though this was not true in our patient.⁴ Serum concentrations of β -HCG and α -fetoprotein are commonly used for detection. While β -HCG is often above the normal range in germ cell tumour histology, α -fetoprotein concentrations are normal as seminoma cells do not produce α -fetoprotein.¹¹

As a result of treatment for extragonadal germ cell tumours, patients may also be at increased risk for pulmonary, coronary and vascular events, and reduced neuromuscular functioning due to treatment.^{12 13} Venous thromboembolism has an incidence rate surpassing 1 per 1000, with a higher risk associated with malignant neoplasm, increasing age, male patients, recent surgery, trauma or hospitalisation. Death within 30 days (30%) and recurrent thrombosis within 10 years (30%) are common

outcomes for patients presenting with thromboembolism. Anti-coagulants reduce the risk of recurrence; however, as soon as therapies are discontinued, the risk of recurrent thromboembolism increases.¹⁴ Our patient's risk factors for venous thromboembolism were direct vascular compression due to the massive mediastinal tumour, hypercoagulability of malignancy and cisplatin chemotherapy.¹⁵ Our patient responded well to anti-coagulant therapy and had no further thromboembolic events.

While a causative effect cannot be demonstrated, we find it intriguing that our patient had childhood exposure to radioactive fallout from the Chernobyl disaster. The literature documents a strong association between nuclear radiation exposure and the development of thyroid tumours.^{16 17} An increased incidence of germ cell tumours has also been reported, although the evidence is not as strong.⁶

The prognosis for primary extragonadal germ cell tumours of the mediastinum is worse than gonadal germ cell tumours. Pure mediastinal seminomas are associated with better outcomes than non-seminomatous tumours. Preoperative cisplatin-based chemotherapy followed by aggressive surgical resection of residual masses is the most common course of treatment, with a 5-year survival rate of 90%.³ The relapse rate approaches 6% after combination chemotherapy and is associated with poor prognosis.¹⁸ Our patient has thus far had a durable complete pathological response to neoadjuvant chemotherapy and did not require surgical intervention, continuing to be free of detectable disease 72 months after therapy.

Contributors AW contributed fully to the clinical data acquisition and analysis and to the authorship of this manuscript. NPS, JFQ and IRMP were directly involved in the clinical evaluation and care of the patient described in this case report. NPS

Patient's perspective

I am very grateful for everyone who made my recovery possible. First of all, I am grateful to my family, especially my wife who became my patient advocate, who researched everything about my condition, read every medical article and study, who knew all the questions to ask the doctors. She was the one who convinced me to go to the hospital, stay overnight and get a blood transfusion when I had a severe infection during my treatment (I was very much opposed to staying at a hospital overnight). My wife took care of me, as well as the rest of our family including our toddler aged 18 months, and continued working full time. The whole process was very physically and emotionally draining for her. Without her, my recovery would not be possible.

Of course, I would like to thank my medical care team. This includes Dr Sandhu, who listened to me when I thought that the combination of my symptoms—while each on its own is not uncommon—was something more than just 'being in my head' or 'insufficient sodium intake', as all the previous doctors had told me. She decided to perform additional testing, which finally led to my diagnosis of the germ cell seminoma and SVC compression.

Also, I am thankful to Dr Quevedo from Oncology, who really cared about me as a patient—a very important quality for a doctor. Dr Quevedo would personally call me on the regular basis to check on how I was doing, including on weekends when he was spending time with his family. During and post-treatment, he always helped triage and coordinate the response to any problem during complications or after any abnormal test results and reassured me when things were ok. And he did that as soon as he possibly could without making me wait or ask, since he knows that waiting during those times can be very stressful.

I appreciate all the help I received from Dr McPhail from Interventional Radiology, who performed the venogram and tried to unblock the SVC. The next day after the procedure, he took the time out of his very busy schedule (I did not have an appointment) in between procedures (he had been doing procedures all day) to show me how all of the collateral vessels had formed to compensate for the SVC compression and to reassure me that everything was ok.

Also, I would like to thank the Oncology nurses who took care of me almost every day during my chemotherapy treatments. They were very proficient in starting intravenous treatments (not an easy task for me) and also were the ones who initially diagnosed the blood clots that I had developed during treatments. One day they alerted me: "your face looks very swollen, you probably have a blood clot and should get it checked out immediately". This, of course, was probably life-saving.

Finally, I cannot think of a better health system than Mayo where my recovery was made possible. Mayo is the best integrated health system, where all healthcare providers from all types and specialties work as a team. I have been to a lot of clinics, but only at Mayo, a doctor can pick up the phone and call another specialist for a quick consult right during the appointment. Only at Mayo, the staff tries as much as possible to make the patient's experience as efficient and as seamless as possible to resolve the patient's problem in as few appointments/visits as possible.

Looking back on my experience, there are a few important points to keep in mind. First, it is important to listen to the patient and evaluate the combination of symptoms as a whole in addition to just looking at each symptom individually. In my case, this was key to diagnosing my cancer.

Second, it is important for both patients and healthcare providers to watch for symptoms of blood clots and know what to do if symptoms are noted as they are common during chemotherapy treatments.

Third, it is very important to inform patients about the risks and symptoms of infection after the start of the chemotherapy treatments. In my case, I had a severe infection and a resulting blood transfusion during the third chemo cycle. Following this infection, we decided to modify the treatment plan and stop the fourth chemo cycle due to good response and high risk of infection.

Also, it is important for patients, families, doctors and caregivers to work together to manage patient stress and to make sure that patients listen to doctors and caregivers. In my case, while the beginning of the treatments were relatively non-eventful, as the treatments progressed, I started experiencing all sorts of severe side effects from the combination of the chemotherapy drugs and the drugs used to manage the side effects (such as anti-nausea drugs or extra white blood cell booster shots, etc). All the side effects such as nausea, severe pain everywhere so that I could not stand or lay, constipation, swelling, fevers, infections, etc made things stressful and made me want to stop the treatments at many different points. So it was important that my wife and the doctors convinced me to continue.

Again, I thank everyone who made my recovery possible.

Reminder of important clinical lesson

developed the concept of this case report, and contributed fully to clinical data acquisition and analysis and authorship of the manuscript. JFQ and IRMP contributed to clinical data analysis relevant to their areas of clinical expertise and contributed fully to the authorship of the manuscript. All authors have read and approved of the manuscript in its entirety.

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Learning points

- ▶ Germ cell tumours may present in extragonadal locations, most commonly the mediastinum.
- ▶ Thromboembolism in young individuals must be evaluated for the possibility of malignancy.
- ▶ In the setting of a mediastinal malignancy, superior vena cava syndrome may be due to thromboembolism or direct compression due to a space-occupying lesion.
- ▶ Pure mediastinal seminomas are associated with better outcomes than non-seminomatous tumours.

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