A Case of pleural solitary fibrous tumour with paraneoplastic hypoglycaemia - Doege-Potter syndrome

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SUMMARY

Pleural-based solitary fibrous tumours (SFT) are rare with incidence of less than 5% reported in literature. It can present as incidental finding on chest imaging or with paraneoplastic symptoms like recurrent hypoglycaemia. Doege-Potter Syndrome refers to solitary fibrous tumour associated with non-islet cell tumour hypoglycaemia (NICTH), as a result of tumour secretion of insulin-like growth factor 2. This is in turn, led by a common driver mutation in solitary fibrous tumours, causes tumorigenesis. Guided core biopsy is often diagnostic of SFT. Pre-operative medical control of hypoglycaemia is often required. Surgery is the definitive treatment, but complete resection might be challenging due to the size and location of the tumour.

INTRODUCTION

Solitary fibrous tumours (SFT) are rare, and they arise from cells in the tissues that support other tissues throughout the body, known as connective tissue. Solitary fibrous tumours of the pleura (SFTP) account for about 30% of all SFTs, while accounting for less than 5% of all pleural based tumours.[1] Patients can be asymptomatic at presentation with incidental finding on the chest imaging, or when symptomatic, present with paraneoplastic symptoms such as recurrent hypoglycaemia. The latter is a manifestation of non-islet cell tumour hypoglycaemia (NICTH), due to tumour secretion of insulin-like growth factors 2 (IGF2). The discovery of the common driver mutation in the pathogenesis of these rare tumours has redefined means for diagnosis by immunohistochemical study and potential molecular targets for adjuvant treatment.[2] Complete surgical resection remains the definitive treatment for SFTP, and surgery can be challenging due to the large size of the tumour.

Here we report a rare case of SFTP associated with NICTH (Doege-Potter syndrome) and discuss its prevalence, pathogenesis, diagnosis, management and follow up of this disease.

CASE PRESENTATION

A 55-year-old previously healthy woman, presented with recurrent hypoglycaemic episodes requiring hospital admissions (serum glucose level ranges 1.9 – 3.9 mmol/L). She also reported weight loss around 10 kg within the past 4 months. During her admission, a large right sided lung mass was noted. There was no respiratory symptom. She does not smoke, and pulmonary TB workup was negative. Physical examination revealed decreased breath sounds on the right and was otherwise unremarkable.

Her chest x-ray (CXR) showed a large opacity occupying the entire right middle and lower zone. Computed tomography (CT) revealed a 14.4 cm x 11.5 cm x 20.0 cm ill-defined heterogenous mass within the right hemithorax with mass effect and compression to right pulmonary artery and lower lobe bronchus (Figure 1).

An ultrasound guided biopsy of the mass was reported as solitary fibrous tumour. Immunohistochemical study shows neoplastic cells which are positive for CD34, STAT6 and CD99, with Ki-67 proliferative index approximately 10%. The cells are negative for CKMNF 116, SMA, CD117 and S100.

Prolonged fasting test was suggestive of NICTH. She had low serum insulin (<1.3 pmol/L), with short synacthen test showed adequate response. Her thyroid function test was normal and blood test for sulfonylurea was negative. She was reviewed by endocrine team and started on raw corn starch and tablet prednisolone 5 mg once daily (OD) for 2 months for her recurrent severe hypoglycaemia. Preop random cortisol was 367 nmol/L.

She subsequently underwent right thoracotomy and excision of the right pleural tumour and intraoperatively, a 1.8 kg, 21 cm × 12 cm tumour with smooth fibrous capsule was excised. On post operative day 3, she was noted to have transient rebound hyperglycaemia, requiring insulin administration. However, it resolved quickly and her blood sugar was back to normal within 1 week post surgery and insulin was taken off. Her post operative recovery was otherwise uneventful and her serum insulin level normalised when checked during her 1 month follow-up.

DISCUSSION AND CONCLUSION

Solitary fibrous tumour is collectively one of the common causes of NICTH, together with carcinomas arising from the gastrointestinal (GI) tract, hepatopancreatic system, fibrosarcomas and haemangiopericytomas.[3] SFTs are rare and they arise from mesenchymal fibroblasts that are found in loose connective tissues of serous membranes in the brain, thorax and abdomen.[4] Up to 30% of SFT can be SFTP.

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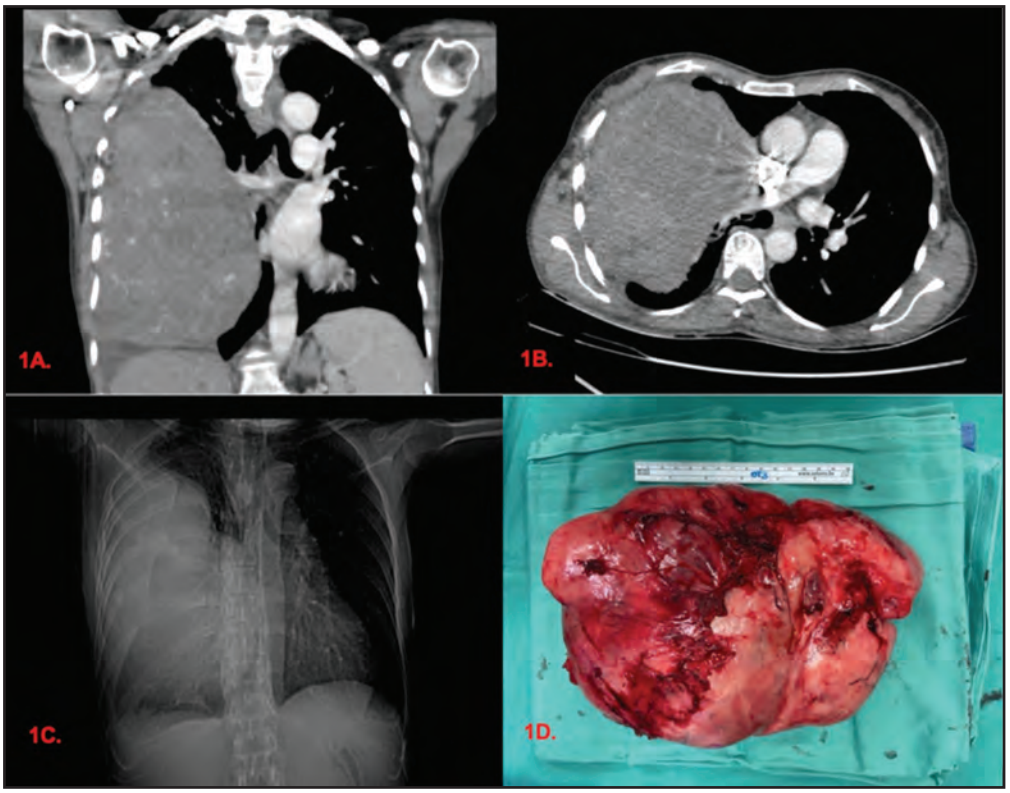

Fig. 1: 1A. Coronal view; 1B. Axial view demonstrating mass compressing on right pulmonary artery. Figure 1C CXR showing mass occupying two third of right lung field. Figure 1D Operative specimen.

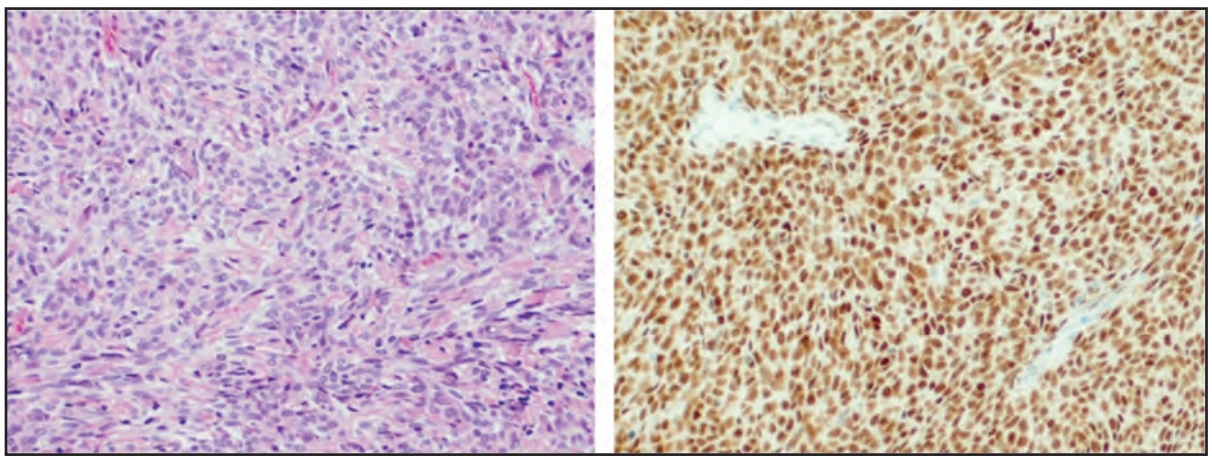

Fig. 2: Histopathological examination of solitary fibrous tumour showing A) Haphazardly arranged spindle to ovoid cells in a variably collagenous stroma (Haematoxylin and Eosin x 200 magnification), B) diffuse nuclear positivity for STAT6 (× 200 magnification).

However, out of all pleural based tumours, SFTP is a rare subset accounting for less than 5%.

SFT manifesting with NICTH is referred to as Doege-Potter syndrome, and SFTP involving the right hemithorax, like in the case of our reported patient, are most commonly associated with this syndrome.[5] The same author reported up to 60% of Doege-Potter syndrome to be associated with malignant SFT, and these are often extra pleural SFTs involving the retroperitoneal or pelvic area, and the meningeal layer.

SFTPs show no sex predilection with equal distribution amongst males and females. They have a peak incidence between 40 and 70 years, with median age at diagnosis in the fifth decade. They are slow growing tumours with low malignant potential. Patient can be asymptomatic until the tumour reaches a large size at the time of diagnosis, with resultant mass effect symptoms. Alternatively in the case of NICTH, patient can present with hypoglycaemic episodes like the ones in this patient.

The NICTH is the result of the tumour secretion of the bigger molecular weighted IGF2. The tumour itself is often well circumscribed and surrounded by fibrous pseudocapsule, with a base that contains big feeder vessels. Grossly, the size of the tumour has been reported to range from a few centimetres to over 40 cm. In this patient, the tumour measures 24 cm x 12 cm x 18 cm, weigh 1.8 kg and has a smooth fibrous capsule. Histologically, haphazardly arranged bland spindled to ovoid cells can be seen embedded in a dense collagenous stroma, with mitosis score of up to 3 per 10 high power fields in the cellular areas. Immunohistochemistry study revealed that the neoplastic cells are positive for CD34, CD99 and STAT6 in our case (Figure 2).

The discovery of the common driver mutation in 2013 for pleural and extrapleural SFTs is a pivotal moment in our understanding of the pathogenesis of these rare tumours. Genetically, it is a result of chromosomal translocation of the NGFI-A binding protein 2 gene (NAB2) to the signal transducer and activator of transcription 6 gene (STAT6).2 This NAB2-STAT6 gene fusion acts as a constituent activator of EGR1 (early growth response 1) targeted transcription and relocates to the nucleus, resulting in cell over proliferations and tumorigenesis. Nuclear STAT6 immunohistochemistry is a sensitive and specific surrogate marker for all fusions.[6]

Workup during initial diagnosis usually starts when patient is brought to the healthcare setup during hypoglycaemic spells. CXR helps to alert the presence of intrathoracic mass, but CT scan is needed to assess the location and relation to adjacent structures beside assessing the tumour size. Magnetic resonance imaging (MRI) may help in delineating diaphragmatic or spine involvement. Positron emission tomography (PET) scan can show presence of distant metastasis in case of malignant SFT.

Guided core needle biopsy is often diagnostic of SFT. However, even the core samples are often inadequate to show enough histological indicators to predict high risk or aggressive tumoral behaviour. These indicators are mainly gathered from histopathological examination and immunohistochemical study of the resected specimen. The definitive management of SFTP is complete tumour resection. Prior to resection, hypoglycaemia can be controlled with dextrose infusion, use of glucocorticoids like dexamethasone, and caloric supplementation.

The surgical principle for malignant SFTP resection is en-bloc resection with a 1 2 cm free margin. Approaches include open thoracotomy and/or sternotomy depending on tumour size and location.[7] Video-assisted thoracoscopic surgery may be used for smaller pedunculated tumour. Due to its often-large size at presentation and depending on the location of the tumour, complete (R0) en-bloc resection might involve partial resection of the adjacent pleura, diaphragm, pericardium or lung, with resultant morbidity. Preoperative embolisation of the feeding vessels for large tumours (>20 cm) is a viable option to reduce the intraoperative blood loss.[8]

SFTs is known to show a variable range of biological behaviour, with up to 15 to 20% showing risk for local recurrence and metastases. It is therefore important for the treating doctors to note that although it is less common for SFTP to be malignant compared to extrapleural SFT, post operative surveillance and follow up should closely take into consideration the World Health Organisation (WHO) risk model for prediction of metastasis of SFTs (original reference[9]). This model takes into account four variables namely the age, tumour size, mitoses and necrosis. A score is assigned under each variable to give a total score that risk stratifies the metastasis-free survival (MFS). It is found that those with low total score (0-3) has a 100% MFS compared to an intermediate/high score (4-7) with 50% MFS at 5 years post operative.[10] Some authors have proposed that increased Ki-67 protein expression, seen on immunohistochemical study, as another reliable indicator for malignant behaviour.

We learned that our patient is in the high-risk category based on the WHO model with a score of 5, and we are following her up long term with close initial surveillance. She is currently disease free within her first-year surveillance. For adjuvant treatment of malignant SFTs, platinum-based chemotherapy like anthracycline has shown limited benefit. Targeted therapy with tyrosine kinase inhibitors has also shown to be ineffective, except for anecdotal report of disease control for refractory NICTH in patient with an unresectable, metastatic SFT.[11] There is no evidence showing radiotherapy to be beneficial in unresectable SFTP. Similarly, in cases of resected SFTPs with margin involvement, tumour recurrence or malignant SFTP, the lack of conclusive evidence favouring adjuvant radiotherapy means any decision on its application should be individualised and guided by multidisciplinary discussion.

There is strong evidence to support long term follow up after complete resection of SFTP. Surveillance imaging should be done at 3 and 6 months after resection, and then yearly thereafter for 10 years.[12] MRI is recommended where possible, to reduce radiation dose.

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