

Solitary Fibrous Tumour of the Pleura Presenting with Refractory Non-Insulin Mediated Hypoglycaemia (The Doege-Potter Syndrome)

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SUMMARY

We report a case of a 61 year-old man who presented with refractory non-insulin mediated hypoglycaemia. A chest radiograph showed a right lung opacity, which was confirmed as a large intra-thoracic mass by computed tomography (CT) of the thorax. CT-guided biopsy with histological examination revealed features of a solitary fibrous tumour of low malignant potential. We discuss the association of solitary fibrous tumour of the pleura (SFTP) with hypoglycaemia, and the management of such rare tumours.

KEY WORDS:

Solitary fibrous tumour of the pleura (SFTP), Doege-Potter Syndrome, Non-islet cell tumour hypoglycaemia (NICTH), Insulin-like growth factor II (IGF-II)

INTRODUCTION

Solitary fibrous tumours of the pleura (SFTP) are rare, slow-growing tumours. So far, only about 800 cases have been reported in the literature^{1,2}. These tumours represent 5-10% of all pleural neoplasms. The majority of these SFTPs are pedunculated masses with benign histology; 12% of them being malignant¹.

Clinical symptoms include cough, dyspnoea, haemoptysis, chest pain and obstructive pneumonitis. Refractory hypoglycaemia (Doege-Potter syndrome) due to non-suppressible insulin-like growth factor II (IGF-II) secretion occurs in less than 5% of patients. Digital clubbing and hypertrophic pulmonary osteo-arthropathy (Pierre-Marie-Bamberg syndrome) have also been described in 10-20% of patients^{1,3}.

We herein report a case of SFTP in occurrence with non-islet cell tumour hypoglycaemia (NICTH). The mainstay of treatment of SFTP is surgical resection. Case reports have documented cure after surgery, with the resolution of hypoglycaemia post-operatively^{4,5}.

CASE REPORT

A 61 year-old Malay gentleman with hypertension, was referred to our Endocrinology Unit for further evaluation of refractory hypoglycaemia in association with a right lung

tumour. He had presented with recurrent hypoglycaemic attacks of 1 year's duration and recent weight loss of about 5kg. He stopped smoking in 2005. There was no prior history of lung disease and he did not complain of any respiratory symptoms. Admission blood pressure was 166/96 mmHg and pulse rate was 100 bpm. Clinical assessment revealed reduced breath sounds and increased vocal resonance in the right lung mid- and lower zones. Systemic examination was otherwise normal; no finger clubbing noted.

Blood tests showed a low IGF-I, and an appropriately suppressed C-peptide and insulin response to hypoglycaemia. Serum cortisol was low as this patient had been on prednisolone a few days prior to the test. IGF-II testing was not available in Malaysia.

Test	Result	Normal
Random Glucose (mmol/L)	1.4	3.5 - 11.1
Plasma C-peptide (pmol/L)	< 166	298 - 1324
Serum insulin (uIU/mL)	< 2	6 - 27
Serum cortisol (nmol/L)	18.9	119 - 618
Serum IGF-I (ng/mL)	41.3	75 - 212

A routine chest radiograph (Figure 1) done at a previous hospital showed a right lung opacity, which was confirmed by computed tomography (CT) of the thorax as a large intra-thoracic mass measuring 19 x 17 x 13cm, associated with a right pleural effusion (Figure 2). CT scan of the abdomen did not show any pancreatic mass.

CT-guided biopsy of the right lung mass was performed. Histopathological examination revealed hypercellularity, with proliferating spindle cells arranged in herring bone and storeiform patterns. There was minimal cytological atypia and single mitosis seen. Immunohistochemically, the cells were strongly positive for CD34 (Figure 3), and negative for desmin, S100, and CD117. These findings were suggestive of a fibrous tumour of low malignant potential, which led us to conclude that our patient had a SFTP.

He experienced repeated fasting and reactive hypoglycaemia in the ward, which was unresponsive to chlorothiazide and verapamil. A trial of oral prednisolone 0.8 mg/kg/day resulted in reduced frequency and severity of hypoglycaemic episodes. He was then referred to the cardiothoracic

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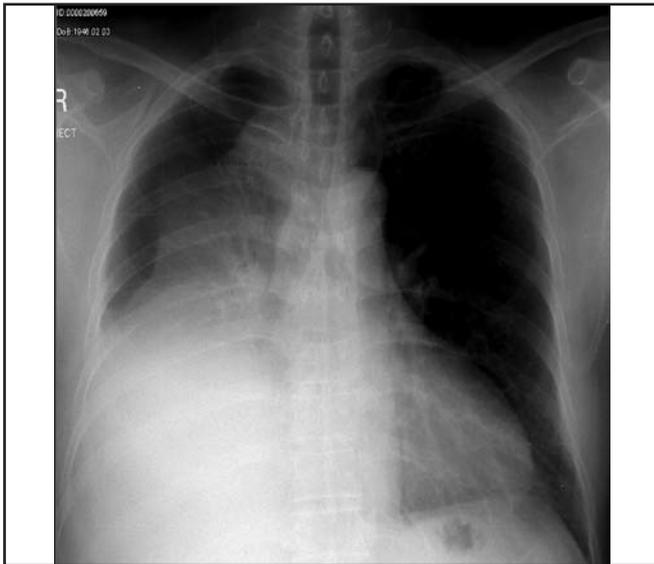


Fig. 1: Chest radiograph showing a homogenous opacity at the right lung middle and lower zones.

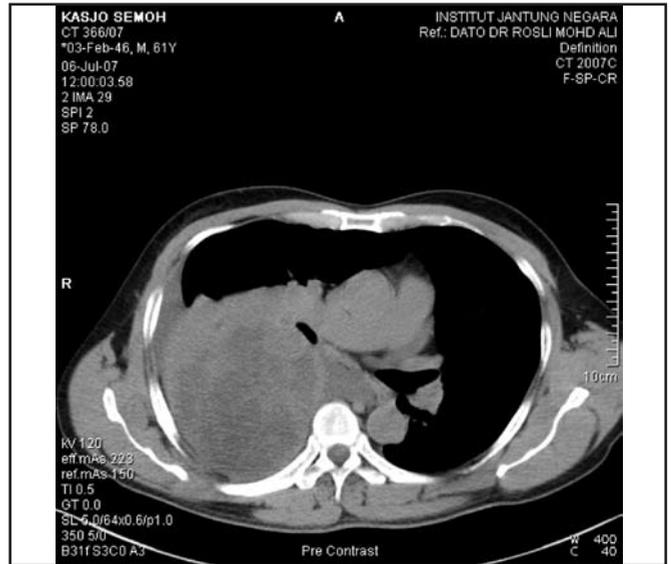


Fig. 2: Large intra-thoracic heterogeneous mass 19 x 17 x 13cm in the right lower hemithorax, abutting the pleura. Cystic/ necrotic areas noted within. Small right pleural effusion.

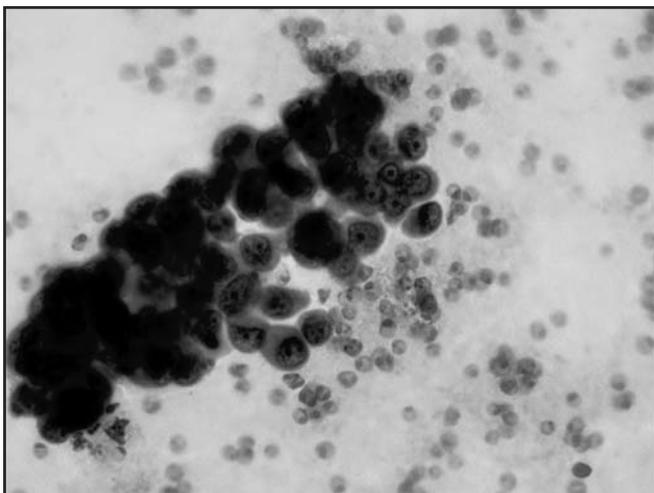


Fig. 3: Immunohistochemical staining for CD34 showing strong positivity in the neoplastic cells, which are stained blue (Original magnification x 500).

surgeons, who deemed the tumour inoperable as a repeat CT reassessment noted further tumour enlargement measuring 24 x 15 x 12cm, with extension to the mediastinum infiltrating into the left atrium. He was subsequently referred for palliative radiotherapy to the right chest and received 30 Grays/ 10 fractions over 2 weeks. Four months post-radiotherapy, he was still experiencing hypoglycaemic episodes despite on low-dose prednisolone 5mg per day. Chest radiographs showed no change in the size of the pleural neoplasm.

DISCUSSION

In 1930, Doege and Potter independently reported the first case of an intra-thoracic fibrosarcoma in association with hypoglycaemia. Refractory hypoglycaemia has been found in

4% of patients with solitary fibrous tumours of the pleura (SFTP), so called non-islet cell tumour hypoglycaemia (NICTH). This hypoglycaemic response is due to tumour overproduction of a higher molecular weight form of IGF-II, termed 'Big' IGF-II 4.

It is often impossible to differentiate between benign and malignant forms of SFTP by radiological imaging^{1,2}. However, radiological features which are suggestive of malignancy include lesions larger than 10cm, associated central necrosis and large pleural effusions. Malignant SFTPs are equally distributed between smokers and non-smokers.

Histological features of a malignant SFTP^{1,3} include:

- high mitotic rate, defined as more than four mitoses per 10 high-power fields
- pleomorphism based on nuclear size, irregularity and nuclear prominence
- bundles of high cellularity with crowding and overlapping of nuclei
- presence of necrosis or haemorrhagic zones
- evidence of stromal or vascular invasion

The mainstay of therapy for all benign and malignant SFTP is complete en bloc resection, with a recommended 1-2cm margin of healthy tissue around the resected tumour^{1,3}. Despite the slow growth and large size at point of diagnosis, these tumours are potentially resectable for cure. Furthermore, resectability has been shown to be the most important determinant of clinical outcome^{1,3}. Excellent five-year survival rates of up to 97% have been reported in cases with complete excision. Total resection normalises the serum IGF-II profile, potentially 'curing' hypoglycaemia^{4,5} and it reduces respiratory symptoms also, improving pulmonary function at the same time.

Local recurrences are extremely rare in benign SFTP, but are not that uncommon in the malignant forms^{1,3}. If recurrence

does occur in benign tumours, possible reasons to consider include incomplete resection, unrecognised malignancy or the occurrence of an unrelated second SFTP, which has been reported in literature³. In cases of recurrence, surgical resection remains the treatment of choice and may lead to prolonged survival.

Few studies report the benefits of radiotherapy and chemotherapy. Suter and colleagues had reported only one patient who underwent radiotherapy after subtotal resection of SFTP and survived more than 20 years. Veronesi and colleagues observed a significant reduction of an inoperable recurrent SFTP with the use of ifosfamide and adriamycin. Our patient had not undergone surgery and failed to respond to radiotherapy with no change in the size of the pleural tumour, hence the persistence of the disease complicated still by occasional episodes of hypoglycaemia.

Literature review shows that the majority of recurrences occur within the first 24 months after resection of malignant SFTP. Approximately half of these recurrences led to deaths during

this period. de Perrot et al. have suggested 6-monthly radiologic surveillance with chest radiography or CT scan during the initial 24 months post-resection and yearly thereafter¹. In view of possible late recurrences associated with death in malignant lesions, long-term follow-up is mandatory.

REFERENCES

1. de Perrot M, Fischer S, Bründler MA *et al.* Solitary fibrous tumors of the pleura. *Ann Thorac Surg* 2002; 74: 285-93.
2. Kohler M, Clarenbach CF, Kestenholz P *et al.* Diagnosis, treatment and long-term outcome of solitary fibrous tumours of the pleura. *Eur J Cardiothorac Surg* 2007; 32: 403-8.
3. England DM, Hochholzer L, McCarthy MJ. Localized benign and malignant fibrous tumors of the pleura: a clinicopathologic review of 223 cases. *Am J Surg Pathol* 1989; 13: 640-58.
4. Balduyck B, Lauwers P, Govaert K *et al.* Solitary Fibrous Tumor of the Pleura with Associated Hypoglycemia: Doege-Potter Syndrome: A Case Report. *J Thorac Onco* 2006; 1: 588-90.
5. Kalebi AY, Hale MJ, Wong ML *et al.* Surgically cured hypoglycemia secondary to pleural solitary fibrous tumour: case report and update review on the Doege-Potter syndrome. *J Cardiothorac Surg* 2009; 4: 45.