The Doege-Potter Syndrome: A Case Of Pleural Fibroma Secreting Insulin Like Growth Factor 2 (IGF-2)

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Citation

Abstract
We present a case of known giant pleural fibroma, which developed symptomatic hypoglycaemia as a late complication, presenting in an unusual manner, necessitating surgical resection. This tumour was found to secrete Insulin like growth factor-2 (IGF-2) which was responsible for the hypoglycaemic episodes. The level of IGF-2 and its ratio to IGF-1 returned to normal after resection of the tumour suggesting that it was the cause of the hypoglycaemia. This is an example of the Doege-Potter syndrome.

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INTRODUCTION
Insulin-like growth factor 2 (IGF-2), a factor stimulating normal cell growth and proliferation, is recognised as a possible mitogen in the pathogenesis in a number of neoplasms. As it lowers blood glucose levels in a similar fashion to insulin it has also been implicated as a cause of tumour associated hypoglycaemia. We report a known case of giant pleural fibroma developing hypoglycaemia as a late complication, leading to successful surgical resection.

HISTORY
An eighty-four year old male presented to his local hospital with a twelve-month history of increasing breathlessness on exertion and fatigue. There was no significant past medical history. A chest x-ray revealed opacification of the right hemi-thorax suggestive of a large right pleural effusion. After aspiration of the effusion (2.2 litres) it became evident that an underlying space occupying lesion was present. (See x-ray figure 1).

A CT guided needle biopsy was performed. Histological sections showed spindle cell proliferation with areas of stromal hyalinisation. The immunostaining profile was negative for cytokeratins, desmin, smooth muscle actin, S100 protein and was positive for vimentin and CD34. These appearances are typical for a solitary fibrous tumour of the pleura.

The patient was managed conservatively as it was felt that
this was a long standing tumour, which since drainage of the associated effusion, was only causing minimal symptoms.

Six months after initial presentation he developed symptomatic hypoglycaemia. This was brought to a head when the patient collapsed at home. On regaining consciousness, he found paramedics from the local ambulance staff standing over him. They had found the patient to be profoundly hypoglycaemic and had administered an injection of intramuscular glucagon which was effective in restoring the patients consciousness. On further questioning the patient admitted to suffering from increasingly frequent dizzy spells, blurred vision and confusion which improved after eating a biscuit or taking a fizzy drink containing glucose.

The patient underwent a battery of biochemical tests. A long synacthen test was normal. His Insulin and C-peptide levels were completely suppressed during these hypoglycaemic attacks and there was no ketone body or sulphonylurea production.

Insulin like growth factor 1(IGF-1) and Insulin like growth factor 2 (IGF-2), were measured and found to be abnormal (see table 1) with a high IGF-2 to IGF-1 ratio. He was started on steroids in an attempt to control his symptoms but this proved ineffective. In view of his increasing symptoms, life threatening hypoglycaemia and failed medical therapy surgical resection was felt to be the only option. Respiratory function tests revealed an FEV1 of 1.21 with an FVC of 1.77 (56% and 53% of predicted). Bronchoscopy as expected from the CT scan showed no endobronchial abnormality. The preoperative CT scan clearly showed the tumour but no recurrence of the pleural effusion.

Figure 2
Table 1: Serum IGF Levels pre and post resection

<table>
<thead>
<tr>
<th>Serum IGF-1 level</th>
<th>Pre operation</th>
<th>Post operation</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.3 nmol/L</td>
<td>19.3 nmol/L</td>
<td>5.0-22.5</td>
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Initially a right thoracotomy was performed through the 5th intercostal space. There was a giant tumour, approximately 22cm in diameter, loosely adherent to the chest wall in places and almost filling the chest. It was impossible to get control medially due to the size of the tumour and after dissecting as much as possible the thoracotomy was closed. Next a median sternotomy was performed. The right pleura was opened and further dissection performed in the right chest. It was still impossible to get safe control of the hilar region and therefore the incision was converted to a T shape with a small anterior thoracotomy.

The vascular pedicle to the tumour arose from the first and second intercostal vessels together with the internal thoracic artery. The mass weighed 2.2kg and was measured at 22cm x 20cm x 8.5cm.

The patient made a very good post operative recovery and was discharged home on the 5th day after operation. He has been followed up for 12 months and has been asymptomatic and found to be normoglycaemic. His IGF 2 (insulin like growth factor 2) levels returned to normal after resection.

DISCUSSION

The Insulin like growth factor family of proteins, including IGF 1 and IGF 2 have been shown to have a role in numerous cellular activities regulating cell proliferation, differentiation and apoptosis. The major site of manufacture of circulating IGF proteins is the liver. Dysfunction of its regulatory functions may result in neoplastic transformation (1). Alternatively regulatory dysfunction may be an end product of neoplastic transformation where these proteins are over expressed, by for instance loss of genomic imprinting –the differential expression of the two alleles of the IGF-2 gene in somatic cells (3).

IGFs secreted by tumours may act in an autocrine or paracrine fashion promoting tumour growth, or on distant tissues exerting an endocrine function. IGFs are normally protein bound, 6 carrier proteins have so far been identified, regulating the activity of IGFs on their receptors. In the absence of disease the ratio of IGF-1 to IGF-2 is constant. In symptomatic tumour associated hypoglycaemia, IGF-2 levels and its ratio to IGF-1, are often found to be elevated. The IGF-2 is thought to bind to insulin receptors activating them and inducing hypoglycaemia. The form of IGF-2 secreted by non islet cell tumours implicated in hypoglycaemia has been widely reported as being of a larger than normal molecular weight (4). This large form IGF-2 demonstrates decreased binding to its serum binding proteins which may allow it to have a different activity profile at a given serum level compared to the usual form IGF-2.

In this case the tumour was large and long standing with hypoglycaemia developing as a late complication. It is likely that these tumours secrete IGF-2 sub-clinically as only a small proportion of pleural fibromas produce hypoglycaemia. Mechanisms by which hypoglycaemia may
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be induced other than IGF activity include consumption of glucose by a large tumour or a failure of compensatory mechanisms to prevent hypoglycaemia.

Hypoglycaemia associated with large non-islet cell tumours is a well documented syndrome and occurs in a wide variety of different tumours. The occurrence of an intrathoracic tumor, with symptoms consistent with hypoglycaemia, was first reported in 1930 by Doege and Potter. Doege reported periods of nervousness, irrationality and incessant talking associated with a thready, weak pulse, which responded to morphine and scopolamine. Interestingly the patients' symptoms also settled with glucose given rectally. The presence of an intrathoracic tumour with symptomatic hypoglycaemia is sometimes known as the Doege-Potter syndrome. Most series of pleural fibromas report hypoglycaemia in between 2-4% of cases, whilst hypoglycaemic coma is exceedingly rare and has only been described once previously. Hypoglycaemia with pleural fibroma is more common in females (occurring three times more frequently), with the majority of tumours causing hypoglycaemia being greater than 10cm and arising in the right hemithorax.

What is striking about this case is the way in which those symptoms came to attention. The patient was known to have a benign tumour. He was seen in the outpatient clinic on a regular basis and had not declared any change in his circumstances. If his episode of collapse had not been mentioned there may have been a further delay in recognising the development of possibly life threatening hypoglycaemia. The rapid intervention of the ambulance service was instrumental in initiating the recognition and treatment of this case of tumour associated hypoglycaemia.

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