ACUTE INTESTINAL PSEUDO-OBSTRUCTION DUE TO MALIGNANT THYMOMA

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ABSTRACT

Acute intestinal pseudo-obstruction has been associated with various diverse aetiologies, including several types of malignancies. Malignant thymoma has never been reported before as a cause of acute intestinal pseudo-obstruction. We report here a case of malignant thymoma presenting as acute intestinal pseudo-obstruction. Existing literature on malignant causes of intestinal pseudo-obstruction is also reviewed and discussed.

Keywords: intestinal pseudo-obstruction, malignant thymoma

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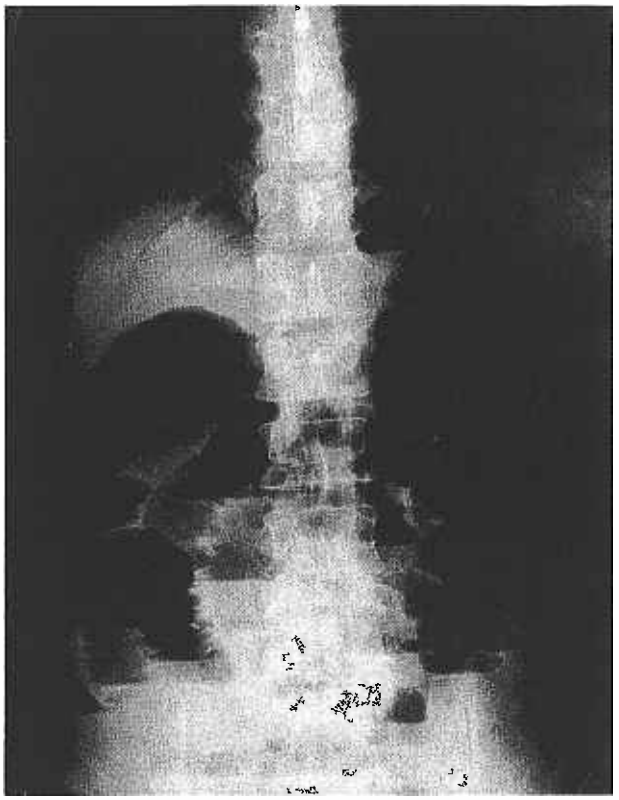
CASE REPORT

A 36-year-old Chinese marketing manager was admitted to the Singapore General Hospital on 2 September 1989 with complaints of difficulty in defaecation for one week followed by absolute constipation for two days. He also had loss of weight of about 5kg over the preceding two weeks. His previous medical history was unremarkable. Clinical examination revealed a thin middle-aged man who was comfortable at rest. Significant findings were in the abdomen which was distended and tympanitic with hyperactive bowel sounds. There was no tenderness or guarding. Abdominal radiograph done on the same day revealed dilated small bowel loops (see Fig 1). Intragastric suction yielded a faeculent aspirate. Serum potassium was normal. A diagnosis of small bowel obstruction was made and an emergency laparotomy was performed that night. Operative findings were that of a dilated gut from the small intestine all the way to the sigmoid colon. There was no signs of any mechanical obstruction. Post-operative recovery was uneventful. He was extubated on the second post-operative day.

Chest radiograph done on admission revealed a right hilar shadow (see Fig 2). Computerised tomogram of the chest showed a large anterior mediastinal mass lying very close to the pericardium. There were no enlarged lymph nodes. There was consolidation of the right lower lobe (see Fig 3). Bronchoscopy did not reveal any mass lesion. A percutaneous needle aspiration biopsy was diagnosed as either a lymphoma or malignant thymoma. Blood cultures grew *Pseudomonas aeruginosa* and *Citrobacter* species which were successfully treated by the appropriate antibiotics.

Fig 1 - Abdominal radiograph showing intestinal obstruction.



Thoracotomy and excision of the anterior mediastinal mass was performed on 4 October 1989. There was a large lobulated anterior mediastinal mass lateralising to the right and measuring 6-7cm in diameter. It was adherent to the right superior vena cava and innominate vein and had invaded the anterior bronchopulmonary segment of the right upper lobe and the adjacent pericardium.The tumour was completely removed together with the invaded lung tissue and pericardium. Histology revealed a lymphocyte predominant variant of malignant thymoma with invasion of the right upper lobe of the lung (see Fig 4 & 5). The patient was able to take full feeds just two days after the operation. More significantly, four days after the thoracotomy and excision of the tumour, for the first time since admission, he was able to defaecate normally. The patient was discharged on 13 October 1989.

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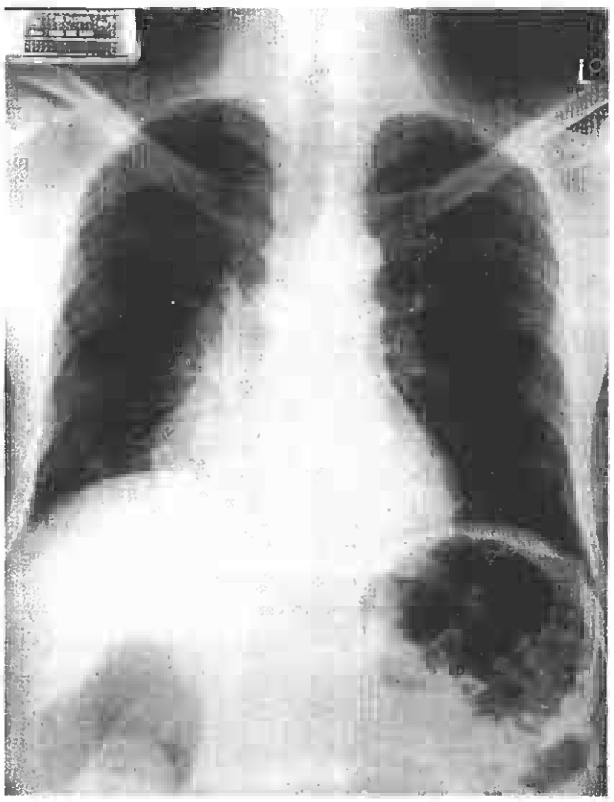
Fig 2 - Chest radiograph showing right hilar mass.



Five days later, he was re-admitted for respiratory arrest after experiencing difficulty in breathing for a few days. He was intubated. At that time he was also noted to have diplopia and proximal weakness of the limbs. Electromyography confirmed the clinical diagnosis of myasthenia gravis. Subsequently he could not be completely weaned off ventilatory support despite maximal therapy with steroids, cytotoxic chemotherapy, radiation therapy and plasmapheresis. He finally succumbed to an aspiration pneumonia and died on 10 April 1990.

DISCUSSION

Our patient presented with a typical history of acute intestinal obstruction which was accompanied by classical clinical and radiological findings. Laparotomy revealed no mechanical cause for the intestinal obstruction. He was later confirmed to have a malignant thymoma. Surgical removal of the thymoma resulted in resolution of the intestinal pseudo-obstruction thus strongly suggesting that the pseudo-obstruction is attributable to the malignant thymoma.

Many diverse aetiologies and associations have been reported in relationship to acute intestinal pseudo-obstruction. However, most of them are of a non-malignant nature. Two collective analyses of 355 cases of acute intestinal pseudo-obstruction from 1948 to 1980 by Nanni et al[1] and 400 cases from 1970 to 1985 by Vanek et al[2] revealed that only 2% and 6% respectively of acute intestinal pseudo-obstruction were attributable to malignancies.

A search through the literature from 1966 (MEDLINE Compact Cambridge) yielded several reports of acute intestinal pseudo-obstruction associated with malignancies. Phaeochromocytoma was reported the most number of time[3-6]. There were also reports of association with small-cell carcinoma[7-11] and carcinoid of the lung[9]. Instances were also recorded of acute intestinal pseudo-obstruction associated with metastatic

Fig 3 - CT scan showing large anterior mediastinal mass adjacent ot the pericardium.

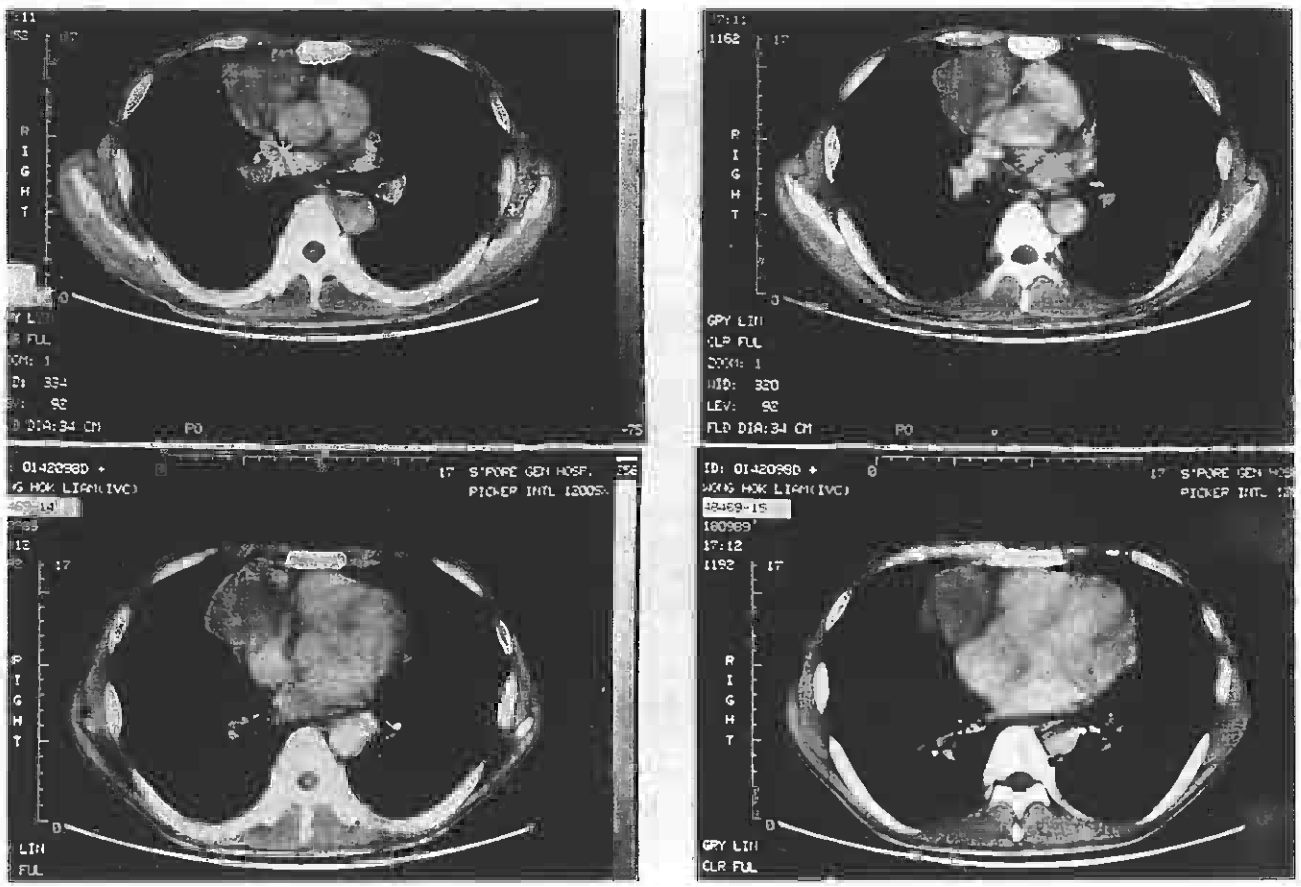


Fig 4 - Lobules of thymoma enclosed by thick fibrous bands (HE X40)

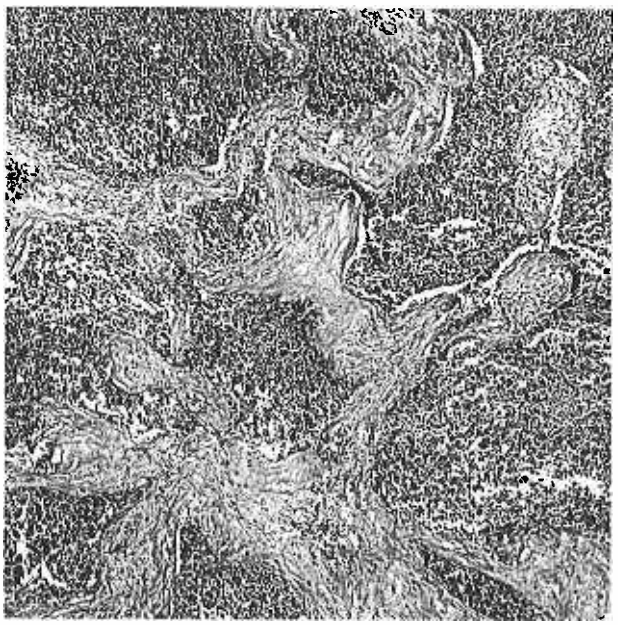
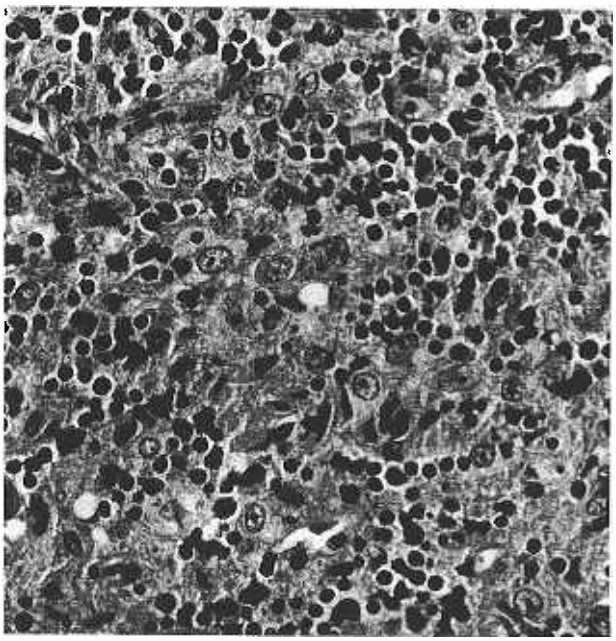


Fig 5 - Thymoma showing admixture of small dark round lymphocytes and pale-staining epithelial cells with prominent nucleoli (HE X200)



malignancy of unknown origin[12,13]. Disseminated malignancies with invasion of the coeliac plexuses tend to present with chronic rather than acute intestinal pseudo-obstruction[14]. Malignant thymoma has never been reported.

In principle, the pathophysiology underlying intestinal pseudo-obstruction may be denervation (as in autonomic neuropathy) or infiltration and destruction of the myenteric plexus[15]. Denervation, which is a well-known paraneoplastic manifestation of malignant diseases, may be due to axonal or myelin destruction secondary to several postulated mechanisms. These include secretion of tumour metabolic products, tumour antigen-antibody reaction, inflammatory response and nutritional deficits[16].

Reported histological studies in acute intestinal pseudo-obstruction associated with small-cell carcinoma of the lung all revealed infiltration and destruction of the myenteric plexuses[7,9,15]. In fact this is also seen in other single-case reports of associations with widespread metastases of unknown origin[12]. Infiltration is by inflammatory cells, especially lymphocytes and plasma cells, with destruction and loss of neurons. There is no infiltration of tumour cells. Most of the plexus may be replaced by Schwann cells, collagen and glial cells. There is no involvement of the muscle layer - therefore the pathology is confined to the myenteric plexus.

Several hypotheses have been put forward. One is autoimmunity from cross-reaction between tumour antigens associated with small-cell carcinoma cells and normal nervous tissue[17]. Similarly pulmonary carcinoid is believed to arise from the same amine precursor uptake and decarboxylation (APUD) cell line as small-cell lung carcinoma, sharing the same antigens[18-21] and thus is also able to cause acute intestinal pseudo-obstruction[9].Another less plausible hypothesis is an opportunistic viral infection in the immunocompromised cancer patient causing the plexus and neuronal destruction. However no cytologic changes in support of this viral infection theory has been seen[9].

Acute intestinal pseudo-obstruction associated with malignant phaeochromocytomas is different in pathogenesis. In a reported case of post-mortem study of the acutely dilated colon, no changes were seen in the histological sections[3]. Only the larger and more actively secreting phaeochromocytomas appear to be associated with acute intestinal pseudo-obstruction[4,6]. This led to the postulation that the colonic immotility is secondary to the large amounts of catecholamines secreted[3-6]. Alpha-adrenergic receptors inhibit release of acetylcholine from postganglionic nerve endings and by blocking these excitatory postsynaptic potentials in myenteric plexus neurones, there is unopposed intrinsic inhibitory neuronal activity[22]. These alpha-adrenergic receptors are also found in sphincteric muscle cells but unlike in myenteric plexuses, they are excitatory[23]. Hence with the excessive secretion of catecholamines by phacochromocytomas there is hyperstimulation of the alpha-adrenergic receptors resulting in ileus and colonic dilatation secondary to intestinal immotility and sphincteric constriction. This postulation has been strongly supported by reports of the pseudo-obstruction resolving within minutes to hours of starting therapy with phentolamine which specifically blocks the stimulation of alpha-adrenergic nerve terminals[3,6].

In our patient the acute intestinal pseudo-obstruction was reversed with removal of the malignant thymoma. The underlying mechanism is therefore likely to be a secretory product of the tumour or related to tumour antigens. Actual infiltration of the plexus by tumour cells is unlikely in view of the reversibility.

Malignant thymomas have been associated with several autoimmune diseases[24-29] and hyperglobulinaemia[30,31]. Our patient's intestinal pseudo-obstruction may be secondary to an autoimmune phenomenon. This autoimmunity may be due to cross-reaction between tumour antigens of the thymoma and neurones of the intestinal plexuses or production of an autoantibody against the neurones. The autoimmunity is unlikely to be directed against unstraited muscles as symptoms would be expected in other organ systems with unstraited muscles (eg pupils, bronchial tree). The removal of the thymoma means cessation of the source of autoimmunity generation and hence reversal of the pseudo-obstruction.

A thymic polypeptide fraction has been isolated by Milcu and workers in 1953. This polypeptide has been shown to

reverse the decreased serum calcium and increased inorganic phosphate in thymectomised rabbits[32]. It is possible that because of the malignant process, there is overproduction of this normal component of the thymus. This would increase serum calcium level and lead to sphincteric contraction thus compounding the intestinal pseudo-obstruction and would reverse with the removal of the malignant thymoma. Unfortunately, serum calcium was not estimated in our patient prior to the laparotomy as pseudo-obstruction was not suspected initially. Subsequently serum calcium levels obtained after the operation were normal.

Symptoms of myasthenia gravis often improve dramatically with removal of a thymus that is non-malignant[33]. However there is often minimal or no improvement if the thymoma is malignant[34-38]. Pseudo-obstruction is not a manifestation of myasthenia gravis as the latter affects only skeletal muscles. Our patient did not have any manifestations of myasthenia gravis when he first presented with acute intestinal pseudo-obstruction although he later developed classical myasthenia gravis. All these reasons are against explaining the pseudo-obstruction and its resolution after thymectomy as part of the myasthenia syndrome.

Alpha-adrenergic overstimulation due to excessive catecholamines (as in malignant phaeochromocytomas) is unlikely to be the case here as there were no other associated signs or symptoms. There is no known association between malignant thymomas and the adrenal medulla.

In conclusion we have reported what we believe to be the first documented case of acute intestinal pseudo-obstruction associated with malignant thymoma. Postulations on the possible mechanism were also put forward. Review of the existing literature revealed that malignancies associated with acute intestinal pseudo-obstruction are uncommon. Pathophysiology of intestinal pseudo-obstruction by the two main types of malignancies reported in the literature is totally different. The gastrointestinal manifestation of intestinal pseudo-obstruction is usually soon followed by death from the primary malignancy.

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