Malignant pancreatic carcinoid tumour

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ABSTRACT

Pancreatic carcinoid tumours are rare, particularly within the paediatric population. The clinical presentation is largely dependent on the functionality of the tumour. Although the tumour is generally slow-growing, surgical resection is still the mainstay of curative treatment. Morbidity is, however, significantly contributed by secretion of excess hormones; in view of this, biotherapy is an important treatment strategy. Octreotide, a somatostatin analogue, has been shown to be successful in both symptomatic control and stability of tumour progression. We report a 12-year-old girl, who presented with hypertensive crisis, and showed good response to a combination of chemotherapy and octreotide.

Keywords: carcinoid tumours, paediatric neoplasm, pancreatic carcinoid tumour

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INTRODUCTION

Carcinoid tumours, a group of neuroendocrine tumours, are generally rare. The annual incidence of pancreatic carcinoid tumours is approximately four per million.[1,2] Up to 70% of these tumours are functional, resulting in a wide range of clinical symptoms, including diarrhoea, malignant hypercalcaemia and hypertension.[2,3] The goal of treatment is reduction of symptoms related to excess secretion of hormone(s) and removal of the primary tumour and metastases, if possible. To achieve this, various treatment modalities have been used, including surgery, chemotherapy and biotherapy. The latter group (such as octreotide and α-interferon) has contributed significantly to the overall management of this condition as it can control symptoms and tumour growth for an extended period of time. Receptor targeted radiotherapy has been shown to be promising, although its use is still very much limited to the research phase.[2] This case report illustrates that although radical surgery offers curative treatment in childhood pancreatic carcinoid, non-surgical treatment modalities should still be considered.

CASE REPORT

A 12-year-old girl was referred to us with symptoms of obstructive jaundice. She also had a one-month history of fever, associated with loss of appetite and weight. Clinically, she was hypertensive and there was a palpable ill-defined mass at the right hypochondrium. Her initial urine catecholamine was elevated and a differential diagnosis of extramedullary phaeochromocytoma was made. Magnetic resonance (MR) imaging of the abdomen revealed a mass at the uncinate process of the pancreas (Fig. 1a) measuring 9 cm × 9.5 cm × 9.5 cm, with displacement of the main portal vein and compression of the inferior vena cava.

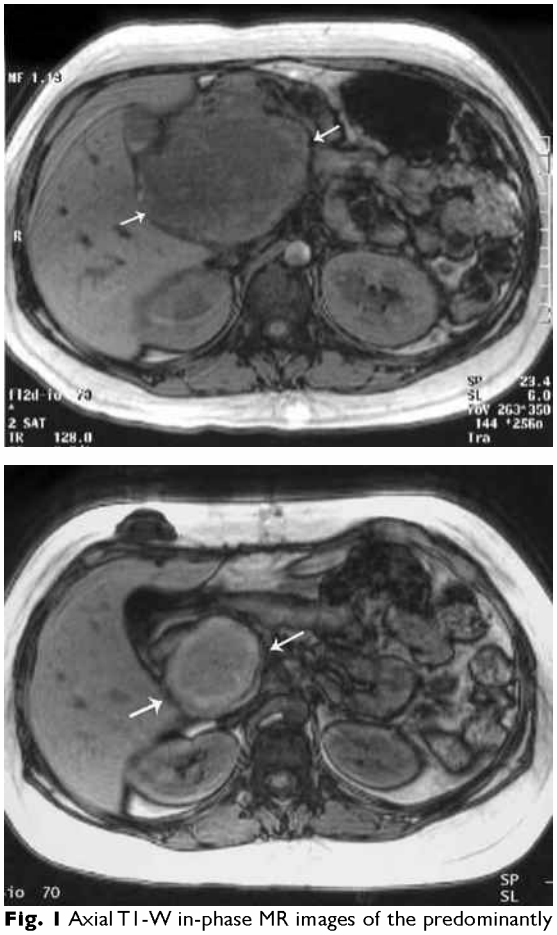

Fig. 1 Axial T1-W in-phase MR images of the predominantly hypointense mass at the head of the pancreas (arrows) (a) before treatment, and (b) on completion of chemotherapy.

Exploratory laparotomy was performed intra-operatively. There was direct tumour infiltration into the mesenteric vein with involvement of the mesenteric and peripancreatic lymph nodes. In view of this, tumour

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resection was not possible, and a palliative triple bypass with tissue biopsy was performed instead. Postoperatively, she developed seizures secondary to hypertensive crisis, with the highest recorded blood pressure measuring 210/120 mmHg. There were also intermittent episodes of early morning sweating and headache. As the blood pressure remained labile, intravenous labetalol, followed by sodium nitroprusside, was administered. Repeat urinary catecholamines were normal.

The histopathology report revealed carcinoid (neuroendocrine) tumour at the head of the pancreas. Immunohistochemical staining was positive for both neuron specific enolase and carcinoembryonic antigen. The patient was started on a titrated dose of subcutaneous octreotide (maximum dose of 75 μg/kg/dose, TDS); her anti-hypertensive medications were gradually converted to oral medications comprising nifedipine, prazosin and labetalol. Staging of the disease was performed. Bone marrow aspiration, bone scintiscan and computed tomography (CT) of the chest were all normal. Tumour markers such as urinary 5-HIAA (hydroxyindoleacetic acid), serum β-hCG and CEA were also normal.

The patient was then started on chemotherapy comprising cisplatinum, doxorubicin, dacarbazine and 5-flurouracil. She received a total of six cycles. Repeat MR imaging of the abdomen, following two cycles of chemotherapy, showed a reduction in tumour volume by 76% (6.3 cm × 5.4 cm × 5.7 cm). Upon completion of chemotherapy (Fig. 1b), a further reduction of 42% (5 cm × 4.8 cm × 4.7 cm) was noted, when compared to the second MR imaging. Throughout this period of time, the anti-hypertensive agents were gradually withdrawn. Octreotide was also withdrawn three months later as she developed persistent colicky abdominal pain and diarrhoea; these are recognised adverse effects. These symptoms resolved upon discontinuation of octreotide. Surgery for tumour debulking was planned, but subsequently declined by the family. Treatment option with radiotherapy was also explored, but in view of the tumour's close proximity to the right kidney and doubtful response, radiotherapy was deemed unsuitable. The latest MR imaging a year after completion of chemotherapy revealed that the tumour volume had reduced by 94% (3 cm × 4 cm × 4 cm), when compared to the first MR imaging on presentation. The patient remains asymptomatic and is presently well.

DISCUSSION

Childhood carcinoid tumours are rare. These neuroendocrine tumours are unique, as affected patients may manifest symptoms typical of carcinoid syndrome, such as paroxysmal flushing, diarrhoea and peripheral vasomotor symptoms. These were seen in our patient. This clinical syndrome is the result of the secretion of biologically active peptides and amines, e.g. serotonin, bradykinin, kallikrein and histamine.[1] Another interesting feature of carcinoid tumours is its multiplicity; the possibility of MEN type I should always be sought in pancreatic carcinoid tumours, especially in the presence of a positive family history and a young age group.[2,3] There was nothing of clinical significance in the family history of our patient.

Carcinoid tumours may be benign or malignant. Its primary location may be anywhere within the digestive tract, in addition to the bronchi, pancreas and ovary. In a clinical review of 81 patients (including adults) by Sabback and O'Brien, the ileum and appendix were the most common anatomical sites, accounting for 31% and 28% of total cases, respectively.[4] Appendiceal carcinoid is the commonest site among paediatric patients. Provided there is no regional lymph node involvement, appendectomy is the mainstay of treatment and its prognosis is excellent.[4] We believe our patient is the first case of paediatric pancreatic carcinoid tumour reported in Malaysia.

In another series of patients with intestinal carcinoids by Yang et al, all 26 patients had evidence of metastatic disease at presentation.[5] Metastases to the lymph nodes, lung, liver and bone have been reported. Generally, the prognosis for malignant carcinoid tumours which have metastasised is poor. However, pancreatic carcinoid tumours show a more indolent clinical behaviour in contrast to their exocrine counterparts. This is in keeping with our patient's clinical profile. It has been reported that the five-year survival rate, without chemotherapy, for a metastasised primary pancreatic carcinoid tumour is approximately 38%.[2]

Treatment modalities include surgery, chemotherapy and biotherapy. Radical surgery is the only form of curative treatment for malignant endocrine tumours; five-year survival rate after an apparent total resection (without metastases) is 72%.[2] Surgical resection was not possible in our patient, and this is not surprising as only 50% of these tumours are actually resectable at presentation.[2] Systemic medical treatment is otherwise palliative. Chemotherapy is indicated if the tumour is deemed unresectable; this was the case in our patient. Streptozotocin (STZ)-based combination, which includes 5-flurouracil and doxorubicin, are widely used as first-line treatment.[3,6] Pancreatic endocrine tumours, which are highly proliferative, are relatively chemosensitive. With the use of STZ-based chemotherapy, partial remission has been reported in up to 40%–60% of patients; even in those with advanced disease, median survival of two years have been reported. This finding is in keeping with our patient's clinical scenario

as there was an overall reduction in tumour volume of 86% one month after total completion of treatment (chemotherapy). To date, chemotherapy has been stopped for the last 31 months, and no further progression of her tumour was detected.

As with treatment of other tumours, the identification of biochemical markers is useful in monitoring therapeutic effect. General markers of endocrine pancreatic tumours include plasma chromogranin A, CA 19-9, CA 50, hCG, and CEA; the latter two markers were, however, normal in our patient. Recently, the proliferation index, Ki67, has been used to help individualise treatment for those with a more malignant profile.[2] In cases of midgut carcinoids, measurement of urinary 5-hydroxyindoleacetic acid is warranted prior to institution of treatment.

Biotherapy, which includes somatostatin analogues and α-interferon, is also widely used. These medications facilitate both symptomatic control and stabilisation of tumour progression.[3] The former has been shown to reduce the secretion of peptide hormones and possibly increase apoptosis. Although studies have shown that up to 36% of cases experience stabilisation of tumour progression, based on CT, tumour regression has not been reported. Octreotide, a stomatostatin analogue, at doses of 100–300 μg/day, provide symptomatic responses in a median of 60% of patients.[1,3] Alternatively, sandostatin-LAR, a slow release parenteral formulation, may be administered on a monthly basis. Our patient showed not only an improvement in her vasomotor symptoms but also better stabilisation of blood pressure following commencement of octreotide. α-interferon is also useful in cases of pancreatic tumour with progression, as a complement to chemotherapy. However, interferon was not used in our patient as there was no tumour progression following commencement of chemotherapy. In conclusion, although radical surgery offers curative treatment in childhood pancreatic carcinoid, our case report illustrates that chemotherapy and biotherapy still play roles in controlling tumour progression for cases that are surgically unresectable.

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