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Intraabdominal Desmoplastic Small Round Cell Tumour In An 11-Year-Old Boy

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ABSTRACT

A case of desmoplastic small round cell tumour (DSRCT) is presented. This aggressive and rare neoplasm predominantly affects males and is almost exclusively intraabdominal in location. It is unique in that neural, mesenchymal and epithelial markers are co-expressed. Despite multi-modal therapy, the prognosis is extremely poor. The present report details the clinical features and typical pathological findings of DSRCT in an 11-year-old boy, who succumbed to the disease 16 months after diagnosis despite multiple chemotherapeutic regimes.

Keywords: small round cell tumour, desmoplastic, desmin

INTRODUCTION

Intraabdominal desmoplastic small round cell tumour (DSRCT) was first proposed as a distinct entity in 1989 when its unique morphological appearance and immunohistochemical features were recognised[1]. It has a predilection for adolescent males and almost always arises from the peritoneum. DSRCT is a rare neoplasm; to date less than 100 cases have been reported world-wide. Typically, the characteristic microscopic finding is the arrangement of the tumour cells in strands and nests of varying sizes surrounded by a highly-collagenous stroma. Immuno-histochemical studies show positivity to epithelial, neural and mesenchyma markers[1]. DSRCT is almost invariably fatal and currently there is no consensus as to its optimal treatment. Awareness of the existence of this entity and its unique characteristics may aid in achieving an early accurate diagnosis . It should also be considered in the differential diagnosis of intraabdominal tumours.

CASE REPORT

An 11-year-old Indian boy, previously well, presented with colicky abdominal pain and weight loss of 2 weeks duration. There was no history of fever or change in bowel habits. On examination, he was cachectic and had a hard, irregular 5 cm X 6 cm mass in the hypogastrium. This mass was non-tender, immobile and non-ballotable. There was no other organomegaly and per rectal examination was normal. The patient's haemoglobin level was 120 g/L, platelets 190 x 10^9/L, leukocytes 8.8 x 10^9/L and ESR 31 mm/hr at presentation. His serum electrolytes and liver function tests were normal. The serum alpha fetoprotein was < 5 IU/L and 3 spot urine tests were negative for vanilyl mandelic acid. The bone marrow examination and trephine biopsy showed no abnormality. Serum ferritin level was 69 µg/L (normal range 29-371 µg/L) and serum lactate dehydrogenase was 178 IU/L (normal range 120-330 IU/L). Computerised tomography (CT) of the abdomen showed a large heterogenous mass measuring 9.8 cm X 4.0 cm in the para-aortic area with extension along the iliac vessels; liver, kidneys, pancreas and spleen were normal (Fig 1). The chest radiograph was normal. .

Trucut biopsy of the abdominal mass revealed clusters of malignant small round cells, separated by a dense fibrous stroma. These cells had small, round hyperchromatic nuclei and scanty cytoplasm. No rosettes were formed . The tumour cells were positive for cytokeratin and neurone-specific enolase but negative for leukocyte common antigen, B and T cell markers. A diagnosis of an undifferentiated round cell tumour was made. The patient then commenced chemotherapy which consisted of adriamycin 35mg/m^2, cyclophosphamide 200 mg/m^2, vincristine 1.5 mg/m^2 and dacarbazine 250 mg/m^2. This course was followed 3 weeks later by cyclophosphamide 200 mg/m^2, cis-platinum 20 mg/m^2 and tenoposide (VM26) 100 mg/m^2. CT of the abdomen done after these courses of chemotherapy showed no reduction in tumour size.

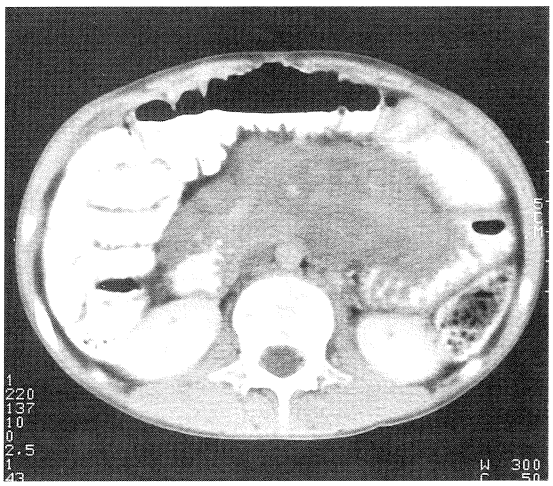

Fig 1 - Computerised tomography of the abdomen showing the irregular tumour mass in the paraaortic area

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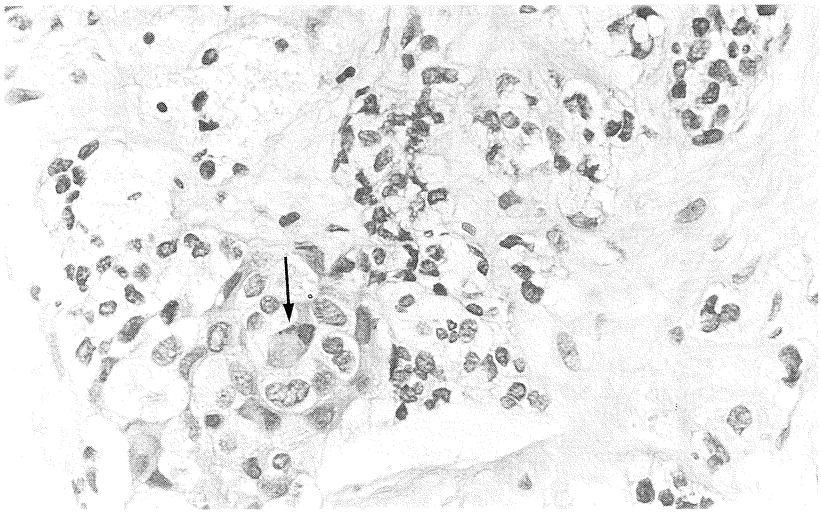

Fig 2 - Mainly small round cells in a desmoplastic stroma with focal rhabdoid differentiation (arrow). H & E X 100 original magnification.

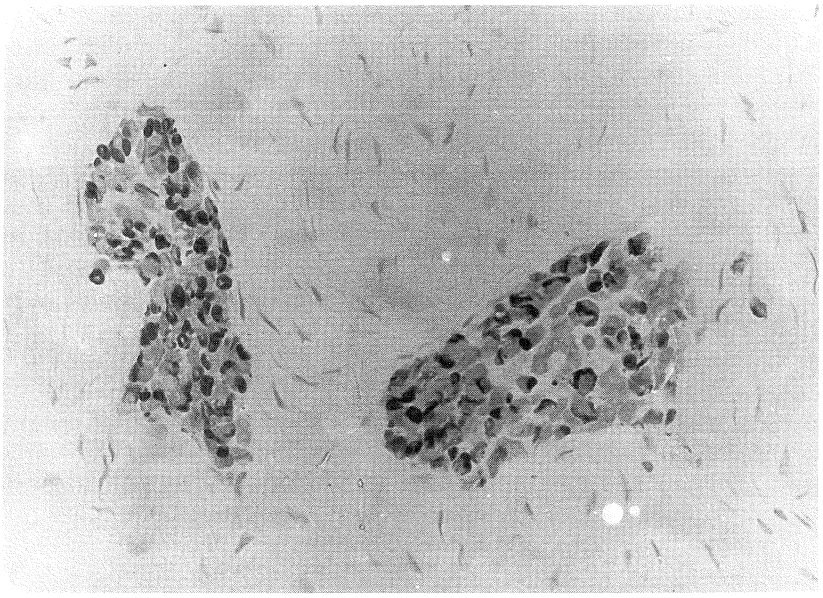

Fig 3 - Positive cystoplasmic immunohistochemical stain for Desmin (Immunoperoxidase stain X 200)

Chemotherapy was then changed to the SIOP Malignant Mesenchymal Tumour Stage IV protocol which consisted of epirubicin 150 mg/m^2, carboplatin 500 mg/m^2 and vincristine 1.5 mg/m^2 followed 3 weeks later with ifosfamide 3 g/m^2, vincristine 1.5 mg/m^2 and actinomycin-D 1.5 mg/m^2. CT done after second course of chemotherapy showed a slight reduction in tumour size and secondary surgery was carried out. However, the tumour was found to be surgically unresectable as it was encasing the major vessels. Another biopsy was done and this time, the tissue showed islands of neoplastic cells in a dense desmoplastic stroma. The cells were pleomorphic, with oval and round nuclei and relatively little cytoplasm. These cells were mixed with larger rhabdoid cells which had eosinophilic cytoplasm and eccentric pleomorphic nuclei. Immunohistochemical stains for neurone-specific enolase, epithelial membrane antigen and desmin were strongly positive (Figs 2 and 3).

A more specific diagnosis of an intraabdominal desmoplastic round cell tumour was made and the chemotherapeutic regime was changed to 3-weekly courses of vincristine 1.0 mg/m^2, etoposide 50 mg/m^2 and cyclophosphamide 1 g/m^2 (VETOPEC). After 2 courses of VETOPEC, CT abdomen showed that the tumour had decreased slightly in size to 6.5 cm X 6.0 cm but Doppler studies showed it to encase and obstruct flow of the superior mesenteric vessels. Encouraged by the response, albeit small, and running out of other chemotherapeutic alternatives, further courses of VETOPEC were given in the hope that adequate tumour reduction could be achieved to render it resectable.

Following the ninth course of VETOPEC, the patient developed severe and prolonged neutropenia and fever, which did not respond to various broad-spectrum antibiotics and granulocyte-stimulating growth factors. Subsequently echocardiography showed presence of a large vegetation around the tip of his central venous catheter in the right atrium. The catheter was promptly removed and vancomycin and oral fucidic acid was administered when his blood cultures yielded Methicillin - resistant *Staphylococcus epidermidis*. He also developed oral herpes simplex which was treated with intravenous acyclovir.

However, he continued to deteriorate and finally expired, 16 months after diagnosis, of septicaemia and unresectable intraabdominal desmoplastic small round cell tumour which was non-responsive to various chemotherapeutic regimes.

DISCUSSION

DSRCT is an aggressive neoplasm which has a predilection for young males. Its location is predominantly intraabdominal and secondary metastases are rare. It presents insidiously with abdominal pain, lassitude or symptoms secondary to bowel obstruction. Of 19 patients with DSRCT reported by Gerald *et al*, 8 presented with abdominal and/or lower back pain and 4 with constipation as the chief complaint[2].

DSRCT belongs to the continously expanding family of small round cell tumours which also includes lymphomas, neuroblastoma, Ewing's sarcoma and Wilms tumour. The most distinctive aspect of DSRCT is the presence of nests and clusters of tumour cells separated by a cellular "desmoplastic" stroma . The cells are remarkably uniform with small round to oval hyperchromatic nuclei and inconspicuous nucleoli . The cytoplasm is eosinophilic and scanty and may contain moderate amounts of glycogen granules.

Ultrastructurally, these tumour cells are compactly grouped within the tumour nodules with discontinuous, or absent, basal lamina. Variable amount of filaments are present within the cytoplasm; usually packed in perinuclear bundles or aggregates. The organelles are made up of mitochondria, many free ribosomes and few lysosomes. Dense-core granules with an average diameter of 111 nm are often present, compatible with a neuroendocrine nature.

DSRCT cells are unique in that they coexpress immunohistochemical reactivity for epithelial (keratin, epithelial membrane antigen), neural (neurone-specific enolase, chromogranin, synaptophysin) and muscle (desmin) markers. Desmin reaction may be diffuse throughout the cytoplasm or in a perinuclear "dot-like" pattern. Positivity may also be shown with S 100 protein and vimentin. They usually are not stained by muscle-specific actin nor by leukocyte common antigen. Flow cytometric studies of DSRCT have shown abnormality in DNA ploidy including aneuploidy and tetraploidy[3]. It is possible that DNA diploid content and low proliferation are indicators of unfavourable biologic characteristics in these tumours and may explain their inability to respond completely to chemotherapeutic agents.

This observation is similar to the poor prognosis associated with tumour DNA diploidy observed in neuroblastoma, Wilms tumour and acute lymphoblastic leukaemia[4]. Considerable interest regarding this tumour has centred on its possible histogenesis. Although DSRCT belongs to the family of small round cell tumours, it is a distinct entity and is not identical (as its ultrastructural features clearly show) to any of the other members. DSRCT shares a resemblance to neuroendocrine carcinoma in the presence of dendritic processes and dense-core granules. However, the cells of DSRCT tend to be larger in size and contain more organelles compared to a typical neuroendocrine carcinoma[3]. Some authors have suggested that DSRCT is an extra-renal form of Wilms tumour given the desmin positivity and rhabdoid features. However, microvilli seen in DSRCT ultrastructurally is absent in Wilms tumour, which also does not express neuroendocrine antigens. Malignant mesothelioma also shares several features with DSRCT eg diffuse peritoneal pattern of spread, presence of epithelial differentiation of tumour cells and that mesothelioma cells coexpress keratin and desmin. However, this malignancy differs from DSRCT in that it expresses muscle-specific actin and does not react to NSE and other neuroendocrine markers.

The pathogenesis of such multi-immunophenotypic differentiation observed in DSRCT remains unknown. A reciprocal chromosome translocation t(11;22)(pl3;ql2) reported recently may be the clue to its origin. This translocation was found in 3 patients with DSRCT, indicating that this could be a consistent abnormal characteristic of this neoplasm[5]. A genomic DNA fragment containing the Ewing's sarcoma and Wilms tumour (EWS-WT1) gene fusion has also been isolated from a DSRCT[6].

The extremely aggressive nature of this tumour leads to its poor prognosis. Usual anti-neoplastic agents used in the management of DSRCT include adriamycin, cisplatinum and cyclophosphamide[1]. Typically, partial response to chemotherapy is seen initially, as in our patient, but this is often followed by uncontrolled albeit local, tumour progression. Schmidt *et al* reported only 1 out of 5 patients with abdominal DSRCT achieved complete remission following use of chemotherapy and alpha interferon. However, this patient subsequently died of veno-occlusive disease of the liver[7]. In the series by Gerald, 15 out of 19 patients died of the disease; 50% of them within a year of diagnosis. There is currently no consensus on the optimal treatment for DSRCT, while radiotherapy has also been shown to be ineffective[2].

Tumour tissue may be obtained via open biopsy at laparotomy or percutaneously. Fine needle aspiration cytology can be diagnostic in the majority of cases, allowing specific treatment to be given to patients with unresectable small round cell tumours without a tissue biopsy[8,9].

The presence of a desmoplastic fibromyxoid stroma as well as the divergent differentiation of cells may explain the constant chemoresistance of DSRCT. Thus it is important that various immuno-histochemical markers be used on biopsied tumour tissue especially if the the microscopic features seem to suggest DSRCT or if the clinician is faced with a problem of an unduly chemoresistant "rhabdomyosarcoma".

Extensive immunohistochemical characterization for all cases of small round cell tumours of the abdomen will ensure that the diagnosis of DSRCT is not overlooked as this tumour is refractory to chemotherapy and early aggressive surgery may be warranted.

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