

Clinics in Diagnostic Imaging (3 I)

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Fig 1 - Frontal abdominal radiograph

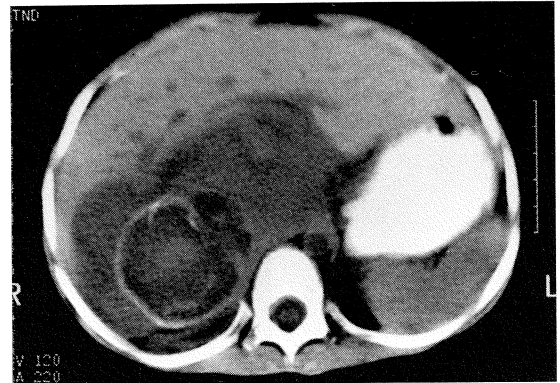


Fig 2a - Unenhanced CT scan of the abdomen at levels of the mid-liver

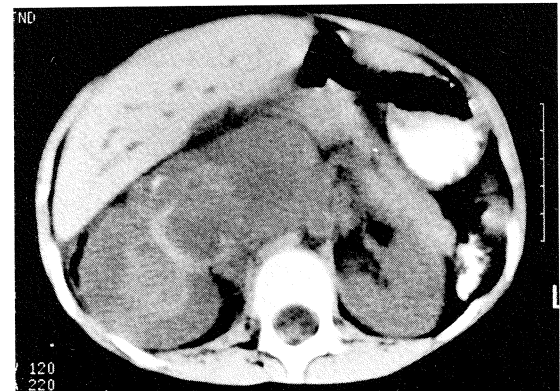


Fig 2b - Unenhanced CT scan of the mid-pole of left kidney

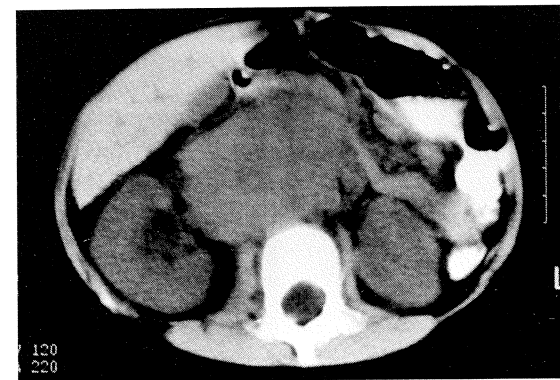


Fig 2c - Unenhanced CT scan of the lower pole of left kidney

CASE REPORT

A 3-year-old girl was admitted with a complaint of epigastric pain for 6 months. The pain was worst at night and had increased in frequency in the recent few weeks. She also had malaise and weight loss over the same period of time. On examination, a hard irregular mass with ill-defined borders was palpable in the right subcostal region of the abdomen. There was no detectable pallor or lymphadenopathy. Complete blood picture, and liver and renal function tests were normal. What do the radiograph (Fig 1) and computed tomography (CT) scans (Fig 2) of the abdomen show? What is the diagnosis?

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IMAGE INTERPRETATION

The plain radiograph shows a soft tissue mass, with fine stippled calcifications, at the right upper quadrant of the abdomen. There is caudal displacement of the bowel gas shadows. No bony lesion is seen (Fig 1). Unenhanced CT shows a huge tumour arising from the right adrenal gland. The tumour is largely hypodense, with areas of necrosis and curvilinear calcifications. There is extension of the tumour mass across the midline (Figs 2a-c). The extent of major vascular involvement is much better appreciated on enhanced CT which shows displacement of the inferior vena cava, pancreas, superior mesenteric vessels and aorta (Figs 3a-c). There is hydronephrosis of the right kidney, consistent with obstruction of the upper right ureter. Imaging features are those of an extensive neuroblastoma arising from the right adrenal gland.

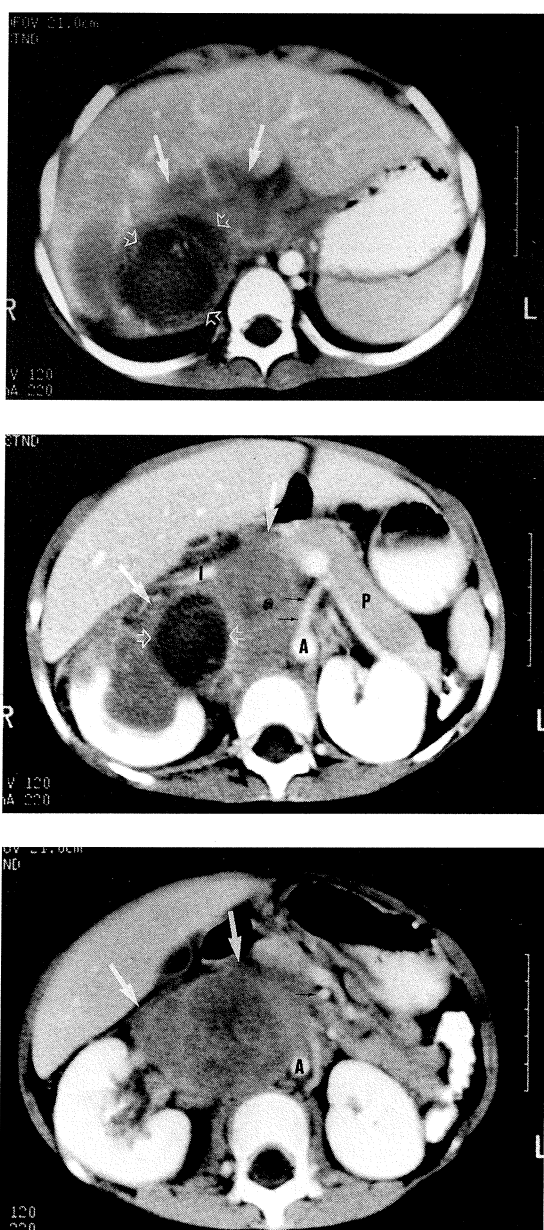


Fig 3 - Enhanced CT scans taken at corresponding levels to Fig 2. The extent of the tumour is well-demarcated (white arrows), with accentuation of the necrotic areas (white open arrowheads). The inferior vena cava (I), aorta (A), superior mesenteric artery (small arrows) and pancreas (P) are displaced by the mass

DIAGNOSIS

Adrenal Neuroblastoma

CLINICAL COURSE

The patient subsequently underwent bone marrow aspiration biopsy which revealed infiltration by malignant cells. Immunophenotyping showed anti-neurofilament antibodies consistent with neuroblastoma infiltration. The urine vanillyl-mandelic acid (VMA) and homovanillic acid (HVA) levels were found to be raised. Diagnosis of stage IV neuroblastoma was made. As the tumour was considered to be inoperable, chemotherapy with the rapid COJEC (consisting of Carboplatin, Etoposide, Vincristine, Cisplatin and Cyclophosphamide) regimen was started. Follow-up CT of the abdomen showed shrinkage of the tumour with disappearance of part of the tumour around the superior mesenteric vessels (Figs 4a-b). No tumour cells were demonstrable on the repeat bone marrow aspiration biopsy.

Laparotomy, en-bloc right nephrectomy and right adrenalectomy with coeliac lymph node dissection were performed (Fig 5). Histopathological examination of the excised specimen showed only necrotic tissue. No viable tumour cell was found. Peripheral blood stem cells were harvested from the patient and cryopreserved. After a course of megatherapy with Melphalan, the stem cells were used for marrow rescue therapy. The child did not have any complications resulting from this therapy. She has been followed-up regularly for three years to date. Regular urine VMA and HVA, and CT scans of abdomen have not revealed any tumour recurrence.

DISCUSSION

Neuroblastoma is one of the most common solid tumours in children. This tumour arises from neural crest cells and may occur anywhere within the sympathetic nervous system. Frequently-involved sites include the adrenal medulla, sympathetic trunk and retroperitoneal sympathetic paraganglia. The majority of these tumours originate in the abdomen, half to two-thirds of which arise from the adrenal gland⁽¹⁾. Differentiation into ganglioneuroma and neurofibroma has been observed clinically. Neuroblastoma is rarely familial but is known to be associated with neurofibromatosis and colonic aganglionosis⁽²⁾. The most important prognostic indicators are age of patient and tumour stage at the time of diagnosis. The 5-year survival for a child under one year of age is 96%, in contrast to 60% for a child older than one year⁽³⁾. In recent years, the importance of histological grade and biological features have been increasingly recognised. These include genetic factors such as DNA ploidy, number of copies of certain oncogenes and deletion of the short arm of chromosome 1, and serum tumour markers such as ferritin, neurone-specific enolase and lactate dehydrogenase⁽⁴⁻⁶⁾.

The presenting features of neuroblastoma depend on the site of the primary disease as well as the presence of metastases. The commonest presentation of the

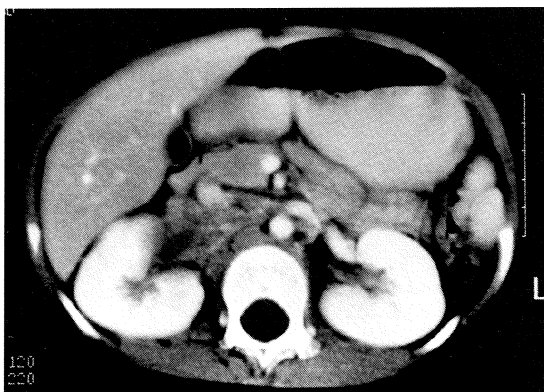
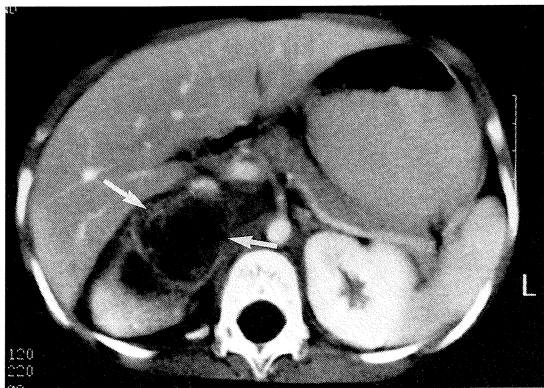


Fig 4 - Enhanced CT scans taken following chemotherapy show marked shrinkage of the tumour, especially of its midline component. Remnant necrotic tumour which is largely confined to the right adrenal gland is arrowed.

primary tumour is an abdominal mass, with associated pain and distension. Abdominal or pelvic tumours may cause urinary obstruction or infection. Many patients present with symptoms due to metastases, which is the first manifestation of the disease process in up to 60% of patients⁽⁷⁾. Non-specific systemic features such as irritability, anorexia, failure to thrive, weight loss, anaemia, fever and bone pain are common. Symptoms due to catecholamines, which may be produced by the tumour, include flushing, tachycardia, excessive perspiration, hypertension and headache. Profuse diarrhoea with resulting severe loss of potassium sometimes occurs. Neuroblastoma is one of the few cancers that can be diagnosed by urine

analysis⁽³⁾. The catecholamines adrenaline, noradrenaline and dopamine are normal biochemical products of the sympathetic nervous system. In neuroblastoma, these hormones are present in excessive quantities, sometimes accompanied by their precursor form, dihydroxyphenylalanine (DOPA).

Treatment depends on the stage of the disease, therefore accurate staging at the time of diagnosis is essential. The International Neuroblastoma Staging System (INSS) was formulated in 1988 in an attempt to combine the three then existing staging systems⁽³⁾. The INSS emphasises particularly tumour infiltration across the midline as a criterium for stage III disease (Table I). Pre-operative chemotherapy is recommended if radical removal of the tumour is not immediately possible (stage III) or if the child has metastases at presentation (stage IV), as in our patient. Intensive multi-drug chemotherapy has been found to be effective for treatment of late-stage neuroblastoma⁽⁸⁾. Megatherapy followed by autologous peripheral blood stem cell transplant has also been shown to be able to improve survival in disseminated neuroblastoma⁽⁹⁾. Cure may be achieved by therapeutically inducing the tumour to mature into a ganglioneuroma or a pheochromocytoma.

Imaging has an important role in the diagnosis and staging of neuroblastomas. It encompasses a combination of modalities, including ultrasound, CT, magnetic resonance imaging (MRI) and scintigraphy. Imaging is used to identify the primary tumour mass, its extent at presentation and for assessment of response to treatment. Ultrasound and CT can be used to guide percutaneous needle biopsy of the primary tumour to obtain a histological diagnosis⁽¹⁰⁾. Radiographs may provide valuable initial information such as the pattern of calcification (present in up to half of the patients), mediastinal involvement and vertebral neural foraminal widening^(7,11).

Ultrasound is often the first imaging modality used to investigate a child with a suspected abdominal mass⁽¹¹⁾. In the right hands, the diagnosis and nature of neuroblastoma can frequently be made on ultrasound alone. This tumour is typically seen as a heterogeneously-echogenic extrarenal mass which pushes the kidney caudally. Neuroblastoma tends to displace the aorta and inferior vena cava anteriorly much more frequently than does Wilms' tumour. The

Table I The International Neuroblastoma Staging System (INSS)

Stage	Criteria
I.	Localised tumour confined to the area of origin; complete gross resection with or without microscopic residual disease; identifiable ipsilateral and contralateral lymph nodes negative macroscopically.
Ila.	Unilateral tumour with incomplete gross resection; identifiable ipsilateral and contralateral lymph nodes negative microscopically.
Ilb.	Unilateral tumour with complete or incomplete gross resection; with positive ipsilateral regional lymph nodes; contralateral lymph nodes negative microscopically.
III.	Tumour infiltrating across the midline with or without regional lymph node involvement; or, unilateral tumour with contralateral regional lymph node involvement; or, midline tumour with bilateral regional lymph node involvement.
IV.	Dissemination of tumour to distant lymph nodes, bone, bone marrow, liver and/or other organs (except as defined in Stage IVs).
IVs.	Localised primary tumour as defined for Stage I or 2 with dissemination limited to liver, skin and/or bone marrow.

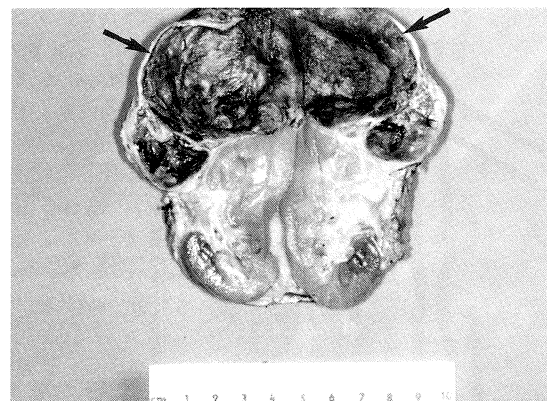


Fig 5 - Resected specimen, which has been bisected, shows extensive necrosis of the right adrenal neuroblastoma (arrows).

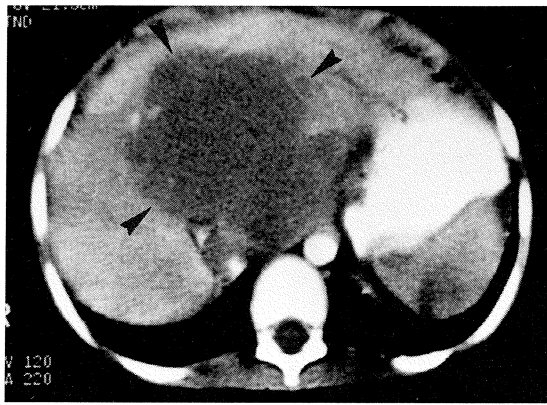


Fig 6a

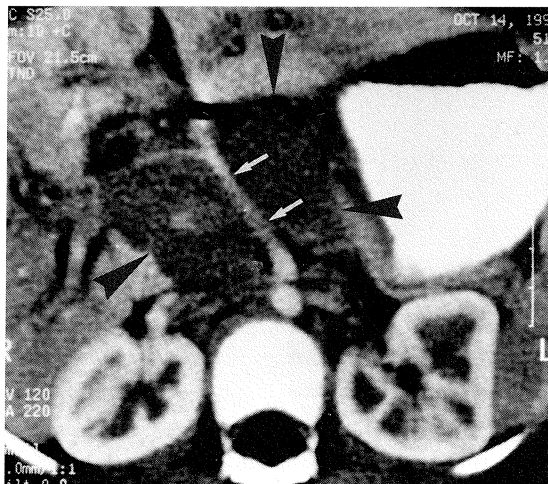


Fig 6b - CT scan of another patient with retroperitoneal lymphoma. Massive lymphadenopathy (arrowheads) is seen (a) compressing the liver and (b) encasing the coeliac axis (arrows).

use of colour Doppler ultrasound is useful in delineating these structures⁽¹⁰⁾. For precise determination of the local extent of tumour and any retroperitoneal, retrocrural or intra-spinal spread, however, CT and MRI are currently the imaging techniques of choice.

On CT scans, neuroblastoma is characteristically seen as a huge lobulated extrarenal retroperitoneal mass. In general, the tumours are isodense or slightly lower in attenuation compared to the surrounding soft tissues and often contain low-density areas corresponding to necrosis or haemorrhage. These tumours usually do not enhance significantly. Calcifications are visible in up to 85% of tumours, with speckled linear or curvilinear calcification in the tumour mass⁽¹¹⁾. The presence of rim calcification, as seen in our patient, is said to be highly suggestive of neuroblastoma⁽¹²⁾. Enhanced CT, particularly if performed using a spiral CT scanner, optimally identifies involvement of vessels such as the aorta, inferior vena cava and their branches, and solid organs such as the liver and kidneys. Vertebral and spinal canal involvement, which occurs in about 15% of patients, is also well depicted on CT⁽¹³⁾. In the pelvis, the tumour may displace the bladder anteriorly, and invade the sacrum and its foramina. Thoracic neuroblastoma usually arises from the paravertebral sympathetic chain, and may be extensive enough to

displace the aorta and mediastinal structures, and involve the spine and ribs. CT is particularly important in evaluation of tumour extension across the midline, that is, in the determination of whether stage III disease is present or not.

The important differential diagnoses of solid paediatric intra-abdominal tumours are Wilms' tumour and lymphoma (Figs 6a-b). On CT, Wilms' tumour is usually seen as a smoothly-marginated mass arising from the kidney. An apparent pseudocapsule, representing compressed normal renal tissue, may be present. In contrast to neuroblastoma, calcification occurs in only about 10% of Wilms' tumours. Tumour extension beyond the renal confines is depicted as a poorly-marginated tumour with irregular or streaky densities extending into the perirenal space. Lymph node metastases, if present, indicate a poorer prognosis. Non-Hodgkin lymphoma is the third most common cancer in childhood, behind leukemia and central nervous system neoplasms. Intra-thoracic disease is seen in 40%-50% of cases. In the abdomen, the para-aortic, mesenteric and splenic hilar lymph nodes are frequently involved.

With its excellent soft tissue contrast resolution, multiplanar capability and lack of ionizing radiation, MRI is probably the single most useful imaging technique for the diagnosis and staging of neuroblastoma^(7,10). The tumour is typically of intermediate signal intensity on T1-weighted sequences and of high signal intensity on T2-weighted sequences. The use of Gadolinium enhancement improves lesion conspicuity⁽¹⁴⁾. Like CT, MRI is useful for defining the exact location and extent of tumour, invasion of adjacent structures, vascular encasement, spinal canal extension and intra-thoracic involvement. Bone marrow metastases may also be assessed by MRI. Limitations of MRI include its poor ability to evaluate calcification, artifacts resulting from patient motion, respiration and bowel movement, and relatively low signal-to-noise ratio. Some of these technical limitations can be overcome by giving general anaesthesia or sedation to young children, cardiac gating and using newer coils such as the phase-array torso coil. With increasing development of faster scanning sequences and improved resolution, MRI is likely to replace CT for the evaluation of neuroblastoma in the future^(7,10).

Bone scintigraphy using technetium ^{99m}Tc methylene diphosphonate (MDP) is far more sensitive than a radiographic skeletal survey for the detection of skeletal metastases^(11,12). Meta-iodo-benzylguanidine (MIBG) scintiscans have been recommended for the initial assessment of the primary tumour and metastatic disease, and in follow-up after treatment⁽⁴⁾. There is however conflicting evidence regarding the relative accuracies of MIBG and ^{99m}Tc MDP scintigraphy in the detection of skeletal metastases^(15,16). The current consensus appears to be that both types of scintigraphy are complementary. The INSS therefore recommends that a MDP bone scan should be carried out if the MIBG scan is negative and may be useful even if it is positive⁽⁷⁾.

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ABSTRACT

A 3-year-old girl presented with epigastric pain and physical examination showed a hard right upper quadrant mass. Urine VMA and HVA were found to be raised. CT scan showed a large mass arising from the right adrenal gland, with necrotic areas and ring calcification. There was midline extension. The diagnosis of neuroblastoma was confirmed by bone marrow aspiration biopsy. As the patient had inoperable stage IV neuroblastoma, she was treated with multi-drug chemotherapy. Follow-up CT scan showed excellent response to the chemotherapy, and the tumour was successfully resected. Harvesting of autologous peripheral bone marrow stem cells, megatherapy with Melphalan, and marrow rescue with the stem cells were effective. The child has been well for three years to date. The clinical and imaging features of neuroblastoma, particularly the role of imaging in staging, are emphasised.

Keywords: neuroblastoma, megatherapy, lymphoma, bone marrow transplant, adrenal neoplasm, neoplasm staging