Atypical manifestation of neurofibromatosis with systemic involvement

Case report

A 22-year-old man, diagnosed with cutaneous neurofibromas since childhood, visited the medical outpatient department following cough and haemoptysis for one month. On examination, there were extensive skin neurofibromas, axillary freckling and *café-au-lait* spots over his back. The patient's initial vital signs were as follows. Body temperature was 35.8°C, blood pressure was 124/68 mmHg, pulse rate was 80 beats per minute and respiratory rate was 16 breaths per minute. The patient's sclerae were not icteric. His neck was supple without jugular vein distension. Chest auscultation revealed clear breath sounds bilaterally. There were no heart murmurs and no special organ abnormalities were detected.

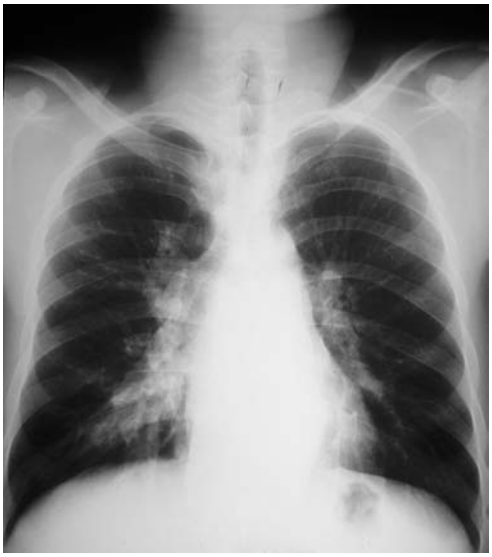

Figure 1
Radiograph of the chest.

Task 1
How would you interpret the chest radiograph?

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Answer 1
Initial chest radiography showed engorged bilateral central bronchovascular marking and hilar shadow.

Under the suspicion of tuberculosis (TB) or lymphoma, the patient was admitted for further evaluation and management. After admission, the haemogram revealed the following. White blood cell count 9.7×10^3 cells per μL with 70.9% neutrophils, platelet count 167×10^3 cells per μL, haemoglobin 14.8 g per dL, and haematocrit 43.1%. The prothrombin time and activated partial thromboplastin time were within normal limits. Aspartate aminotransferase level was 31 U per L, aniline aminotransferase level was 32 U per L, total bilirubin level was 0.4 mg per L, blood urea nitrogen (BUN) level was 15 mg per L, and the creatinine level was 0.9 mg per L. Lactate dehydrogenase (LDH) was 148 IU per L. Subsequent sputum acid-fast stain and TB culture both revealed negative findings.

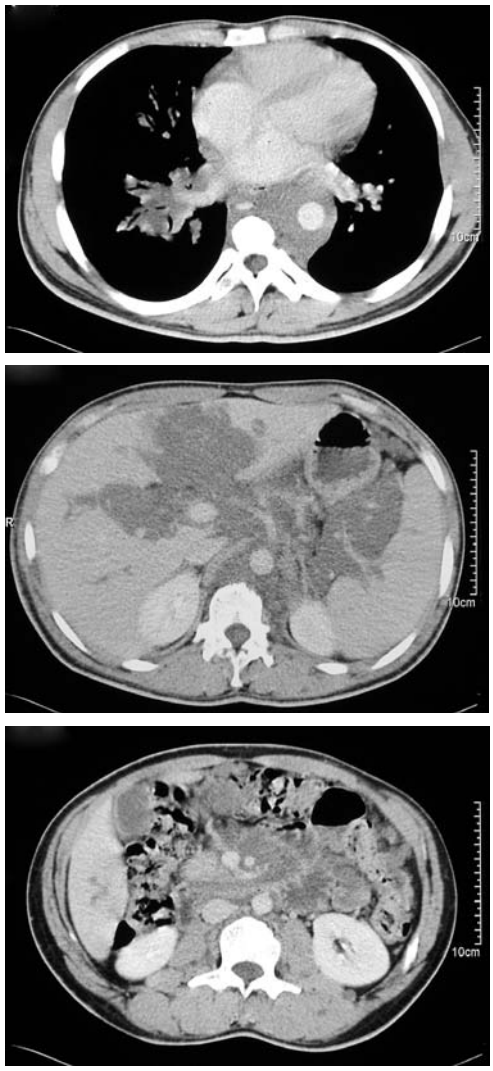

Figure 2
Computed tomography (CT) scans of the chest and abdomen.

Task 2
Interpret the CT scans.

Answer 2
Chest and abdominal CT scan showed loculated water density lesions extending along the space within the mediastinum to the abdominal cavity. Perihilar, parabronchovascular (more on the right lower bronchus), paravertebral, perisplenic, retroperitoneal and bilateral psoas muscles were also involved. In addition, extensive low-attenuation masses in the hepatic hilum and retroperitoneum were found.

Abdominal ultrasonography revealed infiltrative hypoechoic masses around the portovenous system and intrahepatic portal branches. There were no enlarged lymph nodes in the mediastinum or abdomen. A neck nodule and liver biopsy were performed.

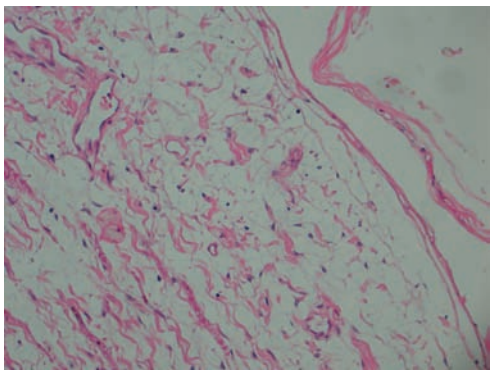

Figure 3
Biopsy histopathology.

Task 3
Describe the histological findings.

Task 4
What would your diagnosis be?

Answer 3
Histopathology shows spindle-cell proliferation with wavy nuclei, tapered ends in the fibrotic collagenous stroma and myxoid background.

No obvious lymph node or liver tissues were detected. Differential diagnosis includes neurofibroma, solitary fibrous tumour, fibromatosis and gastrointestinal stromal tumour (GIST). The immunohistochemistry displayed diffuse strong immunoreaction of S-100 protein and strong reaction for CD34, but was negative for CD117 (c-kit).

Answer 4
Plexiform neurofibroma was diagnosed.

After symptomatic treatment, cough and blood-tinged sputum subsided. No deformities or discomfort were noted, and since surgical intervention was not immediately indicated, patient follow up was handled by the outpatient department.

Discussion

Neurofibromatosis type 1 (NF1; von Recklinghausen's disease) is a relatively common autosomal-dominant neurocutaneous disorder characterised by abnormal skin pigmentation (*café-au-lait* spots and axillary freckling), cutaneous and plexiform neurofibroma, skeletal dysplasias and Lisch nodules. The genetic abnormality in neurofibromatosis has been localised to the *NF1* gene on chromosome 17, which is a tumour suppressor gene in some cell types [1, 2].

This progressive disorder affects all races, all ethnic groups and both sexes equally. Neurofibromatosis is one of the most common genetic disorders the birth incidence of NF1 lies between 1 in 2,500–3,300 and its prevalence in the population is 1 in 5,000 [3]. Neurofibromatosis has two genetically distinct forms: NF1 and NF2. The effects of neurofibromatosis are unpredictable and have varying manifestations and degrees of severity. There is no known cure for either form of neurofibromatosis, although genes for both NF1 and NF2 have been identified. Currently, neurofibromatosis has no treatment other than the surgical removal of tumours, which may sometimes recur. Approximately 50% of those affected with neurofibromatosis have a prior family history of the disease. In the present case, the patient's

grandfather had the same disease. Sporadic cases may perhaps arise due to germ cell mutation [4].

The typical characteristic of NF1 is neurofibroma, of which there are three clinically and histologically distinct types: cutaneous, subcutaneous and plexiform. Nodular neurofibromas arise in peripheral nerves at any site and, although they cannot infiltrate surrounding tissues, they can grow to an enormous size and give rise to the classic thoracic paraspinal dumbbell tumours. Plexiform neurofibromas are usually congenital and are present in about 30% of patients with NF1. Plexiform neurofibromas are often poorly circumscribed, locally invasive, nonmetastatic tumours variably composed of Schwann cells, fibroblasts, and other cell types [5]. They are usually solitary and only 9% of patients with plexiform neurofibromas have multiple lesions, which are located on the trunk, extremities, head and neck. In the current patient, however, multiple involvement was noted in major organs, such as the liver and lung parenchyma.

In about 2–16% of patients, nodular and plexiform neurofibromas transform into malignant peripheral nerve-sheath tumours, which are the major cause of morbidity and mortality in NF1 [6].

Gastrointestinal abnormalities and symptoms in patients with NF1 are reported to occur in ≤10–25% of patients [7]. GISTs usually occur in patients with NF1 after the appearance of cutaneous manifestations. Leiomyoma, neurofibromas, ganglioneuroma and schwannomas have been described. Typical CT features of GISTs include a round, well-defined, heterogeneously enhancing mass. The enhancement pattern is heterogeneous and rim-like with central areas of hypoattenuation [8]. GISTs are defined by their immunohistochemical expression of CD117 (c-kit). In the current patient, the findings on the abdominal CT scan were distinctly different from those produced by of GISTs and the pathology was negative for CD117. Patients with neurofibromatosis may demonstrate soft-tissue attenuation at contrast-enhanced CT findings; low attenuation is characteristic and is seen in ≤73% of all cases [9]. Similar findings were noted in the present case, the mesentery and retroperitoneal lesions of the abdominal CT scan were possibly due to neurofibroma involvement.

It is suggested that a medical evaluation for anyone with neurofibromatosis should include a family history review and examination of the patient's family tree. Routine check-ups for adults with NF1 generally include, in addition to standard physical evaluation, an examination of the skin, blood pressure, vision and hearing, and examination of the spine for scoliosis. Attention is given to any mass that is enlarging rapidly or causing new pain. Most importantly, although neurofibromas are benign tumours, NF1 represents a major risk factor for the development of malignancy, particularly malignant peripheral nerve sheath tumors, optic gliomas, other gliomas and leukaemias [10]. The above should, therefore, be kept in mind for the malignant component of the NF1 phenotype; one of the few life-threatening complications. There is currently no information about the association between the incidence of malignant change and the multiple areas of involvement.

In summary, this case report details a rare presentation of simultaneous occurrence trunk distribution and major organ involvement of neurofibromas. In addition to the clinically diagnostic criteria of NF1, used in some cases, imaging findings were inconclusive, and biopsy and subsequent pathological analysis were needed to confirm a diagnosis.

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