

## A Case of a Patient with Neurofibromatosis Type I Presenting with Abdominal Pain

A 56-year-old gentleman presented to the emergency department after sustaining a fall secondary to an episode of giddiness. He was noted to be hypotensive in the ambulance and subsequently gave a history of non-specific abdominal pain for duration of 1 week. Imaging studies including an abdominal radiograph and a computed tomography (CT) of the abdomen and pelvis (CTAP) were performed to investigate his abdominal pain.

What do the abdominal radiograph (Fig.1), axial and coronal sections of the CT abdomen and pelvis (Figs. 2A, 2B and 2C) show? What is the diagnosis of the abdominal mass?

- A. Intra-abdominal abscess
- B. Carcinoid tumour
- C. Lymphoma
- D. Gastrointestinal stromal tumour (GIST)
- E. Leiomyoma



Fig. 1. Abdominal radiograph obtained at the time of presentation.

### Findings and Diagnosis

The abdominal radiograph (Fig.1) reveals gaseous dilatation of the small bowel loops. Axial (Figs. 2A and 2B) and coronal (Fig. 2C) sections of the CTAP demonstrate a large thick-walled complex mass with gas and fluid debris within (white asterisks), closely related to the small bowel (dashed white arrow). Pneumoperitoneum and gross free fluid are evident. Innumerable cutaneous soft tissue nodules (white arrows) are also noted along the abdominal wall on the abdominal radiograph and CTAP, in keeping with the patient's known underlying neurofibromatosis type 1 (NF 1). Serum investigations revealed elevated values of the patient's total white cell count ( $22.0 \times 10^3/\mu\text{L}$  [4.0-11.0]), C-reactive protein (60.9 mg/L [ $<3.0$ ]), procalcitonin (11.68 ug/L [0.00-0.50]) and lactate (7.39 mmol/L [0.50-2.20]). The patient underwent explorative laparotomy in view of the pneumoperitoneum, which was indicative of a perforated hollow viscus.

Intraoperatively, a small bowel tumour was found to be arising from the mid jejunum with involvement of the adjacent ileum, dome of the urinary bladder, peritoneum and sigmoid mesocolon. The tumour was necrotic and there was evidence of perforation with large amounts of haemoperitoneum. Resection of the small bowel tumour was performed. Histology of the mass revealed a spindle cell subtype gastrointestinal stromal tumour (GIST) of the small bowel with central cystic cavitation. Immunohistochemistry stains of the mass were positive for CD 117, DOG-1 and CD 34, and negative for desmin and S100, compatible with GIST. Notwithstanding the tumour's low mitotic activity (0-1 mitosis/5 mm<sup>2</sup>), the risk of progressive disease in this patient was considered high after taking into account the tumour's anatomic site (small bowel) and large size (13 cm).

In this particular case, the initial differential diagnoses considered were intra-abdominal abscess versus small bowel tumours given the appearance of the mass on CT and patient's raised inflammatory markers. However, note was made of an earlier CT study performed 5 years ago with similar findings. Hence, a small slow growing bowel malignancy was considered a more likely differential than an intra-abdominal abscess. Although carcinoid tumours, lymphoma and leiomyomas involving the small bowel

Answer: D

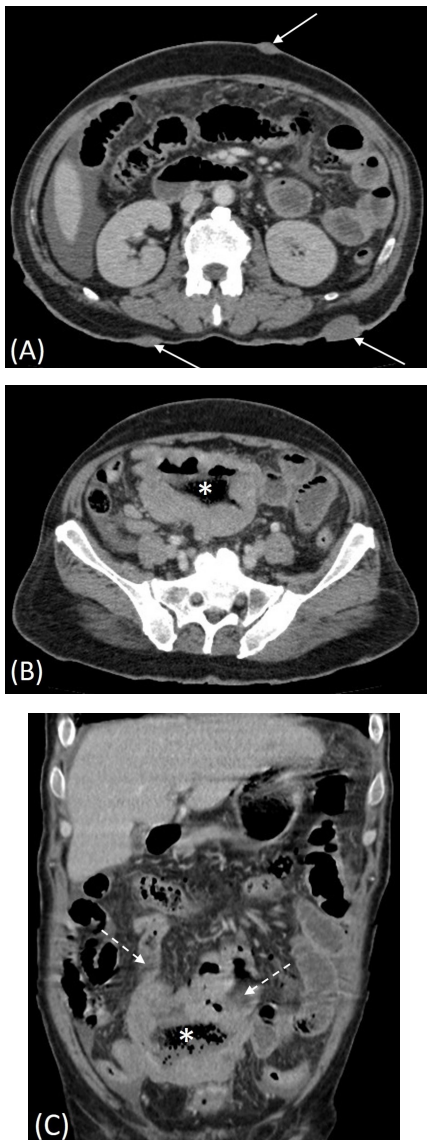


Fig. 2. Axial (A and B) and (C) coronal sections of the patient's CT of the abdomen and pelvis obtained on the same day following the abdominal radiograph.

are more common, a small bowel GIST was considered as the primary preoperative differential diagnosis in this case, after taking into consideration the indolent nature of the mass, the absence of significant intra-abdominal lymphadenopathy, as well as patient's history of NF 1 and its known association with GIST.

## Discussion

Neurofibromatoses refer to 3 genetically inherited disorders, which are clinically and genetically distinct diseases. They include NF 1, neurofibromatosis type 2 and

Schwannomatosis. These 3 conditions are grouped together because they share certain clinical features, however it is important to distinguish them from the others as they differ in their natural history, complications and management. They do not evolve into one of the other forms during the course of the disease.<sup>1</sup>

NF 1 also known as Von Recklinghausen's disease or peripheral neurofibromatosis, is the most common form of neurofibromatosis. The disease bears the name of Friedrich von Recklinghausen (1833-1910), a German pathologist, who was not the first to report the disease but the first to recognise that the characteristic peripheral neurofibromas developed from nervous tissue. It has an incidence of 1 in 3000 births and prevalence of 1 in 4000-5000.<sup>2,3</sup>

The NF 1 gene has been identified on chromosome 17q11.2 and the protein product termed neurofibromin acts as a tumour suppressor.<sup>4</sup> Hence, alterations in the NF 1 gene result in this disease. This gene has one of the highest spontaneous mutation rates in humans and about 50% of those patients with NF 1 do not have a family history.<sup>5</sup> When a positive family history is present, NF 1 is inherited as an autosomal dominant disorder.

Due to the large size of the NF 1 gene and lack of mutation hot spots, it is not practical to use mutation analysis as the initial tool for identifying NF 1.<sup>5</sup> The diagnosis of NF 1 is hence based on the presence of at least 2 of the major clinical criteria established by the National Institutes of Healthcare (NIH) Consensus Development Conference in 1988.<sup>5</sup> The major diagnostic features of NF 1 include café au-lait patches, neurofibromas, skin-fold freckling, iris Lisch nodules, optic pathway glioma and bony dysplasia. Macrocephaly, short stature and cutaneous angiomas are minor diagnostic features of the disease.<sup>2</sup> It is often difficult or impossible to establish the diagnosis of this disease based on the above characteristic clinical features in young children, as these features may not be entirely present at birth and tend to accumulate with age.<sup>1</sup>

The more commonly encountered manifestations of NF 1 include neurological (plexiform neurofibromas, malignant peripheral nerve sheath tumour (MPNST), optic and non-optic nerve gliomas), cardiac (congenital heart disease particularly pulmonic valvular stenosis), vascular (renal artery stenosis, cardiovascular and cerebrovascular disease), and orthopaedic (scoliosis, pseudoarthrosis, bowing of the tibia) disorders.<sup>2</sup>

The median age at death among NF 1 patients is approximately 15 years earlier than would be expected amongst the general population, and about a third of them die from complications before the age of 45 years. The most common causes of premature death in NF 1 patients are namely vasculopathy, MPNST and central nervous system tumours.<sup>1</sup>

Gastrointestinal manifestations of NF 1 include visceral neurogenic tumours, GIST and neuroendocrine tumours. The reported frequency of gastrointestinal manifestations of NF 1 in previous studies ranges from 5% to 25%.<sup>5</sup> Clinical symptoms include abdominal pain, dyspepsia, vomiting, anaemia, malaena, hematemesis, hematochezia, intussusception, volvulus, small bowel obstruction, fever and abdominal mass.<sup>6</sup> The gastrointestinal manifestations related to NF 1 usually present much later in life than the cutaneous manifestations of the disease. Previous studies have shown that approximately 2.5% of NF 1 patients on regular follow-up develop gastrointestinal complications requiring surgical intervention at a median age of 40 years.<sup>5,6</sup>

The association of GIST with NF 1 has been increasingly described in the medical literature and they represent the most common gastrointestinal manifestation of NF 1.<sup>4,5</sup> In all reported cases thus far, GIST occurring in patients with NF 1 have been localised to the small bowel, and not uncommonly associated with other synchronous GIST tumours or other types of intestinal neoplasms. These patients most commonly present with abdominal pain and bleeding.<sup>4</sup> GIST tumours occurring in patients with or without NF1 are identical in histology and immunophenotype. The distinguishing feature of GIST in patients with NF 1 is that it predominates in the small bowel and their tendency for multiplicity. GIST originates from or near the muscularis propria of the intestinal wall and may display intramural, intraluminal or extraluminal extension. Intratumoral hemorrhage, necrosis and degeneration are also often present.

Histological studies of small bowel GIST most often reveal spindle cell morphology with numerous skeinoid fibres.<sup>5</sup> Immunohistochemical demonstration of CD 117 and CD 34 positivity distinguishes GIST from leiomyomas and leiomyosarcomas.<sup>4,7</sup> There is no difference between the biologic behaviour of GIST in patients with or without NF 1 and the tumours can be benign, malignant or have uncertain malignant potential.<sup>4</sup> This notwithstanding, most NF 1-associated GIST tumours commonly present with small tumours with low mitotic activity (<5/50 high-power fields) and generally follow a benign clinical course.<sup>5</sup>

Radiologically, the imaging features of GIST in patients with or without NF 1 are similar. These tumours appear as a heterogenous enhancing mass with areas of haemorrhage and/or cystic change. They are intramural in location and can either extend intraluminally simulating a polypoidal mass or exophytically into the mesentery.<sup>4</sup>

## Conclusion

NF 1 is the most common of the phakomatoses. Due to the varied clinical manifestations and predisposition of

the NF 1 gene for spontaneous mutation, many with the disease present with no pre-existing diagnosis or positive family history.

Although less commonly encountered when compared to the neurological, cardiac, vascular and orthopaedic complications of this disease, it is important to be aware and recognise the gastrointestinal manifestations of NF 1 such as the small bowel GIST reported in our case, as this will aid both the referring clinician and the reporting radiologist in making a presumptive diagnosis of this disorder on imaging.

## REFERENCES

1. Friedman JM, Gutmann DH, MacCollin M, Riccardi VM. Neurofibromatosis: phenotype, natural history and pathogenesis. Baltimore, MD: John Hopkins University Press;1999. p. 169-81.
2. Ferner RE. Neurofibromatosis 1. *Eur J Hum Genet* 2007;15:131-8.
3. Fortman BJ, Kuszyk BS, Urban BA, Fishman EK. Neurofibromatosis type I: a diagnostic mimicker at CT. *Radiographics* 2001;21:601-12.
4. Levy AD, Patel N, Dow N, Abbott RM, Miettinen M, Sobin LH. From the archives of the AFIP. Abdominal neoplasms in patients with neurofibromatosis Type 1: radiologic-pathologic correlation. *Radiographics* 2005;25:455-80.
5. Agaimy A, Vassos N, Croner RS. Gastrointestinal manifestations of Neurofibromatosis Type 1 (Recklinghausen's disease): clinicopathological spectrum with pathogenetic considerations. *Int J Clin Exp Pathol* 2012;5:852-62.
6. Behranwala KA, Spalding D, Wotherspoon A, Fisher C, Thompson JN. Small bowel gastrointestinal stromal tumours and ampullary cancer in Type 1 neurofibromatosis. *World J Surg Oncol* 2004;2:1.
7. Miettinen M, Lasota J. Gastrointestinal stromal tumours: pathology and prognosis at different sites. *Semin Diagn Pathol* 2006;23:70-83.

Shi Yuan Wang, <sup>1</sup>MBBS, FRCR, Tien Jin Tan, <sup>1</sup>MBBS, FRCR

<sup>1</sup>Department of Radiology, Changi General Hospital, Singapore

Address for Correspondence: Dr Wang Shi Yuan, Department of Radiology, Changi General Hospital, 2 Simei Street 3, Singapore 529889.  
Email: wshiyuan@yahoo.com.sg