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Case Report

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Pancreatic adenocarcinoma in a Sri Lankan patient with neurofibromatosis 1

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ABSTRACT

A 27-year-old Sri Lankan man with Neurofibromatosis-1 (NF-1) [MIM:162200] who presented with vague abdominal pain associated with loss of weight and appetite for 1-year duration is described. He had multiple cutaneous neurofibromas, café-au-lait macules and bilateral Lisch nodules. An abdominal contrast-enhanced computed tomography scan showed a mass lesion in the retro pancreatic region with mild enhancement. Diagnostic laparotomy showed multiple liver metastases. Liver biopsy showed an immune morphology which is compatible with deposits of ck17 and ck19 weakly positive adenocarcinoma which led to the probable diagnosis of a pancreatic carcinoma. Genetic testing identified a germline heterozygous pathogenic variant in exon 12 of the *NF-1* gene [NM_001042492.3: c.1307C>A]. The substitution creates a nonsense variant at codon position 436, which changes a Serine to a premature stop codon in the NF-1 protein [NP_001035957.1: p. Ser436Ter]. Patients diagnosed with NF-1 may rarely develop malignancies including pancreatic neuroendocrine tumors and pancreatic adenocarcinomas.

Keywords: Neurofibromatosis-1, Neuroendocrine tumor, Pancreatic adenocarcinoma, von Recklinghausen's syndrome

INTRODUCTION

Neurofibromatosis-1(NF-1) [MIM:162200], also known as von Recklinghausen's syndrome, is a multisystem genetic disorder with an incidence of 1:3000 individuals. It is inherited as an autosomal dominant disease but 50% of patients do not have any family history and present with *de novo* pathogenic variants in the *NF-1* gene located on chromosome 17q11.2 region. NF-1 presents with multiple cutaneous neurofibromas which arise from the neurilemmal sheath, café-au-lait macules, Lisch nodules, optic gliomas and axillary freckling. It is also associated with bone abnormalities such as scoliosis and fibrous dysplasia of long bones, and malignant transformation of neurofibromas. Loss of production or reduced function of the 2,485 amino acid protein "neurofibromin" which is a tumor suppressor encoded by the *NF-1* gene is responsible for the wide spectrum of clinical

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manifestations. *NF-1* pathogenic variants lead to uncontrolled cell proliferation resulting in the development of benign and malignant tumors, including tumors of the nervous system and gastrointestinal tract (1-5). About 1-2% of endocrine tumors are associated with autosomal dominant genetic conditions like Multiple Endocrine Neoplasia type 1 (MEN-1), von Hippel Lindau (vHL) syndrome, NF-1 and tuberous sclerosis complex (TSC) (6-11). Herein, we report a rare case of pancreatic adenocarcinoma arising in a patient with NF-1.

CLINICAL REPORT

A 27-year-old Sri Lankan male presented with a history of loss of appetite and loss of weight associated with vague abdominal pain and early satiety of 1-year duration. There was no history of blindness or hypoglycemia. The family history is significant for NF-1 and his father who has NF-1 was diagnosed with pancreatic carcinoma at the age of 61 years.

Clinical examination revealed a body mass index of 20 kg/m² and he had mildly icteric sclera. He had multiple cutaneous neurofibromas spread all over the body and a few café-au-lait macules with the largest measuring 7 cm in diameter. Ophthalmological examination showed bilateral Lisch nodules with normal fundus and preserved vision (Figure 1A-B). He had no axillary freckling, lymphadenopathy or organomegaly. Neurological, cardiovascular and respiratory system examinations were unremarkable.

Initial blood investigations were normal including alkaline phosphatase and corrected calcium apart from elevated total bilirubin (29.9 micromoles/l). Subsequent upper gastrointestinal endoscopy detected a hiatus hernia, and antral gastritis with an ulcer of 1.5cm at the duodenal junction. Histopathology of that ulcer was reported as unremarkable. Contrast-enhanced computed tomography (CECT) scan of the abdomen showed a mass lesion in the retro pancreatic region with mild enhancement and 2 neurofibromas in the right inguinal region and left gluteal region.

After that he failed to attend medical service as his father had been diagnosed with pancreatic cancer and underwent surgical resection of the tumor. However, he could be able to turn up to the service five months following his father's death. He had a follow up CECT scan of the abdomen with chest and pelvis done 5 months after the initial scan which showed that the size of the primary lesion was marginally increased with encasement of the superior mesenteric artery on its course which made the tumor unresectable (Figure 1C). Magnetic resonance imaging (MRI) scan was not performed as he had shrapnel of a shell blast injury in his lower limb which was difficult to remove by surgery.

He was found to have multiple liver metastases with no peritoneal or anterior abdominal wall lesions during diagnostic laparoscopic assessment (Figure 1D). The liver biopsy showed an immunomorphology which is compatible with deposits of ck17 and ck19 weakly positive adenocarcinoma, which led to the probable diagnosis of a pancreatic carcinoma.

Patient is currently undergoing chemotherapy with oncological follow up.

Subsequently he underwent genetic testing where genomic DNA was extracted and sequenced using the SureSelect® Human All Exon V6 kit on an Illumina® HiSeq® 4000 Next Generation Sequencer. A heterozygous pathogenic variant in exon 12 of the *NF-1* gene [NM_001042492.3: c.1307C>A] was identified. The substitution creates a nonsense variant at codon position 436, which changes a Serine to a premature translational stop codon in the NF-1 protein [NP_001035957.1: p. Ser436Ter]. This variant is predicted to cause loss of normal NF-1 protein function through either protein truncation or nonsense-mediated mRNA decay. Heterozygous loss of function of the *NF-1* gene is an established disease mechanism in NF-1.

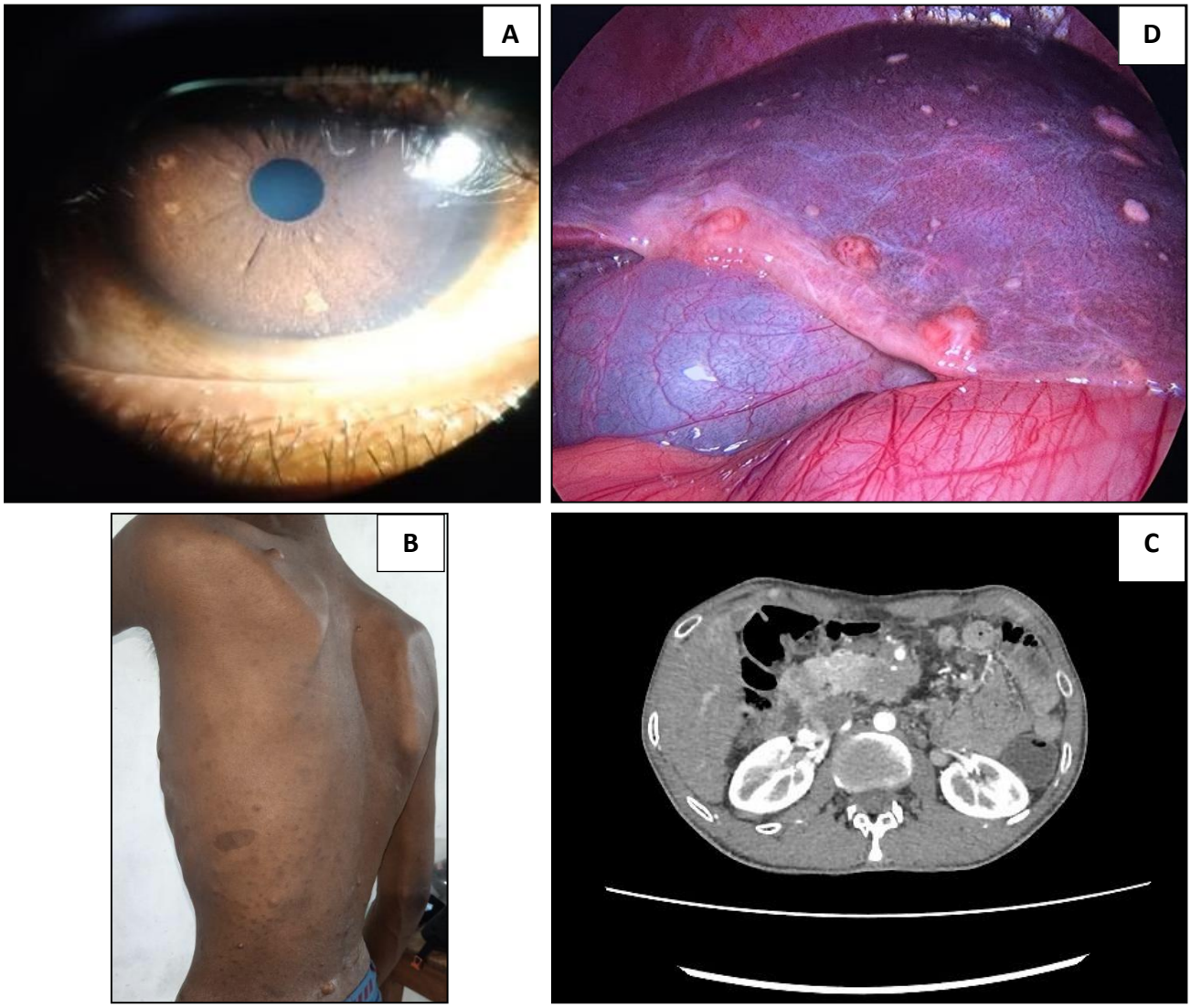

Figure 1: Photographs of the proband showing A) Lisch nodules; B) Café-au-lait macules and cutaneous fibromas on the back of the trunk; C) Contrast-enhanced computed tomography scan of the abdomen showing retro-pancreatic mass with encasement of superior mesenteric artery; D) Laparoscopic view of multiple liver metastasis

DISCUSSION

The neurofibromin protein acts as a tumor suppressor by inhibiting the activity of ras guanosine triphosphatase-activating protein which regulates cell proliferation and differentiation. It also interacts through a signaling pathway with tuberin, the *TSC2* gene product, that regulates mTor, which is a serine-threonine kinase that regulates cell proliferation (10). The association of NF-1 disease with malignant neurogenic neoplasms due to dysfunction of the neurofibromin protein is well established, but there are some reported cases of non-neurogenic neoplasms associated with NF-1 as well.

About 48% of the duodenal somatostatinomas (6), and 23% of ampullary carcinoid tumors are caused by NF-1 (15). Cases of pancreatic somatostatinomas among NF-1 patients is reported to be sixteen times less common than that of duodenal somatostatinomas (6). Among the pancreatic neuroendocrine tumors, around 1-2% of cases are associated with an inherited disorder such as MEN-1, vHL, NF-1 and TSC, in decreasing order of frequency (10).

So far, very few cases of pancreatic adenocarcinoma associated with NF-1 have been reported (13) in the literature. Yamamoto *et al.* reported a case of moderately differentiated pancreatic adenocarcinoma with liver metastases and humoral hypercalcemia of malignancy associated with NF-1 (12). Although dysfunction of neurofibromin due to pathogenic variants in the *NF-1* gene may affect the development of pancreatic neuroendocrine tumors in patients with NF-1, further investigation is required to clarify whether the association is coincidental or due to the *NF-1* gene variations.

In conclusion, pancreatic carcinoma is a rare association of NF-1 and early suspicion and diagnosis with active management is essential.

Author declaration

Authors' contributions:
Study concept and design: T.K. and N.D.S..; Acquisition of data: V.S.; Analysis and interpretation of data: V.H.W.D., and G.A.; Drafting of the manuscript: T.N., and N.M.; Patient Management: V.S., V.S., S.N.

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The authors declare that there is no financial or non-financial conflict of interest.

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Statement on data availability:
The data that supports the findings of this study are available in the supplementary material of this article.

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