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Case Report

Pheochromocytoma and Gastrointestinal Stromal Tumors in a Patient with Neurofibromatosis Type 1: A Rare Triple Malignancy

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Abstract

Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disorder associated with an increased risk of benign and malignant tumors. The concomitant association of pheochromocytoma and gastrointestinal stromal tumor (GIST) remains rare. We report the case of a 57-year-old patient who had been monitored for NF1 for 26 years and operated on for pheochromocytoma, who consulted for chronic epigastric pain associated with anemia. Endoscopic, radiological, and anatomopathological investigations led to a diagnosis of multiple high-risk duodenal-jejunal GISTs. Despite a surgical indication combined with imatinib treatment, the patient refused treatment and died one year later. This observation highlights the rarity of this dual tumor association in NF1 and underscores the importance of systematic, multidisciplinary monitoring of these patients to enable early diagnosis and treatment.

Introduction

Neurofibromatosis type 1 (NF1), or Von Recklinghausen disease, is a rare autosomal dominant genetic disorder that predisposes individuals to the development of benign or malignant tumors. Although pheochromocytoma and gastrointestinal stromal tumors (GIST) are the most common, their concurrent occurrence is considered unusual.

We describe the case of a 57-year-old patient with neurofibromatosis type 1 associated with a gastrointestinal stromal tumor and pheochromocytoma.

Case Presentation

A 57-year-old patient who had been monitored for type 1 neurofibromatosis for 26 years, revealed by the presence of café-au-lait spots and cutaneous neurofibromas (Figure 1), and who had undergone surgery for a pheochromocytoma one year ago.

He consulted for persistent epigastric pain that had been developing for five years, associated with anemia. Physical examination revealed a patient with a PS of 0, stable hemodynamically and respiratorily, with multiple rounded skin nodules of varying sizes scattered across the trunk and abdomen. These lesions are

raised, soft to firm in consistency, and clinically consistent with cutaneous neurofibromas. Abdominal examination revealed epigastric tenderness, with no palpable mass. Furthermore, neurological examination was normal.

Upper gastrointestinal endoscopy revealed an ulcerative-budding process suspected of malignancy at D3 (Figure 2). Pathological examination revealed tumor proliferation composed of spindle cells organized in bundles, without major atypia or abundant mitoses. Immunohistochemical study showed strong positivity for CD117 (c-KIT) and DOG1, with variable expression of CD34, confirming the diagnosis of high-risk GIST.

The abdominal scan showed two tumor processes affecting D4 and the angle of Treitz measuring 80×74 mm extending over 93 mm and 77×64 mm extending over 84 mm with exophytic development enhanced heterogeneously after contrast injection, consistent with GIST given the context. Anteriorly and laterally, they are in contact with a few jejunal loops, the left colon, and the anterior abdominal wall, with no signs of invasion. Medially, they are in contact with the inferior mesenteric artery and vein, with no signs of invasion. Posteriorly, they are in contact with the vertebral plane of the 1st-3rd lumbar vertebrae, the abdominal aorta, the renal pedicle, and the inferior mesenteric vein without signs of invasion, with the presence of multiple subcentimeter lumboaortic and iliac primitive lymph nodes.(Figure 3)

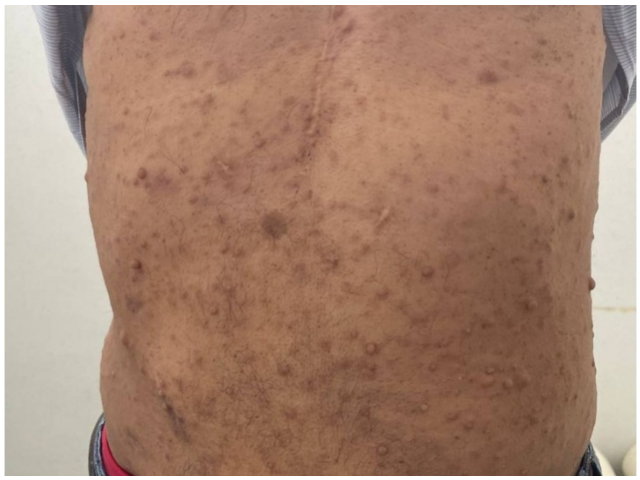

Figure 1 : Clinical photograph showing cutaneous manifestations of neurofibromatosis type 1, including multiple neurofibromas

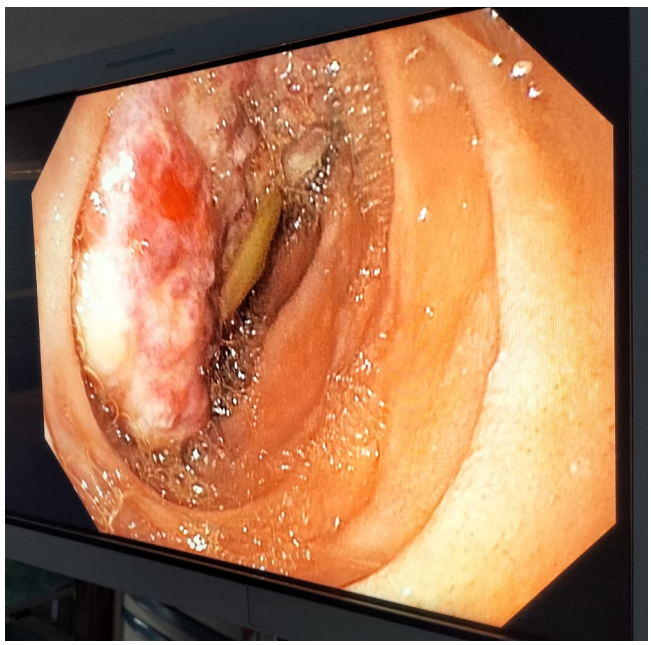

Figure 2: Upper gastrointestinal endoscopy showing an ulcerative and exophytic lesion suspicious for malignancy in the third portion of the duodenum (D3)

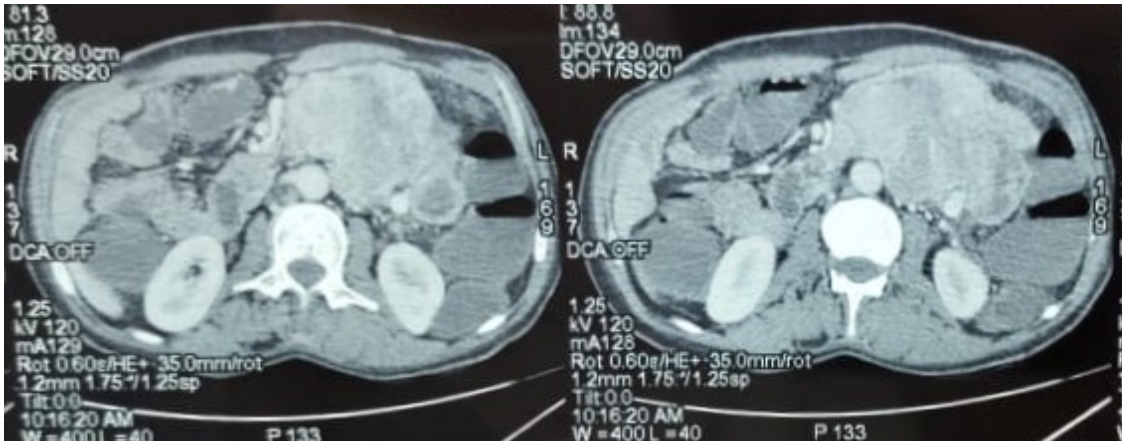

Figure 3: Contrast-enhanced abdominal CT scan revealing two tumoral masses arising from the fourth portion of the duodenum (D4) and the angle of Treitz, suggestive of gastrointestinal stromal tumors

Furthermore, there were no lesions on the chest CT scan.

After discussion at a multidisciplinary team meeting (MDT), surgical removal of the digestive masses (GIST) was proposed, combined with perioperative treatment with Imatinib. The patient refused all medical and surgical treatment and died after one year.

Discussion

Neurofibromatosis type 1, or Von Recklinghausen disease, is an autosomal dominant genodermatosis caused by a germline mutation in the NF1 tumor suppressor gene located on chromosome 17 [1]. This pathological entity predisposes individuals to the development of benign tumors, known as neurofibromas, as well as malignant tumors [1]. Its prevalence is between 1/3000 and 1/6000 and its incidence between 1/2558 and 1/3333 [1]. However, nearly half of the NF1 gene mutations responsible for the disease are sporadic [2].

Although dermatological lesions are often the most prominent feature, NF1 is a disease that affects multiple organs. It is clinically characterized by the triad of café-au-lait spots, cutaneous neurofibromas, and neoplasms of the peripheral and central nervous systems. Diagnosis is primarily clinical and is based on the NIH (National Institutes of Health) criteria established in 1988 and revised in 2021 by the HAS [2]: at least two of the following criteria must be met: café-au-lait spots, axillary/inguinal lentigines, neurofibromas, Lisch nodules, optic pathway glioma, specific bone lesions, or a direct family history.

In our case, the diagnosis of NF1 was made based on the presence of more than six café-au-lait spots, multiple cutaneous neurofibromas, and no known family history.

NF1 is associated with an increased risk of cancer and a reduction in life expectancy of approximately 10-15 years compared to the general population. As a result, regular monitoring of the disease is essential [2]. The co-occurrence of pheochromocytoma and GIST in patients with NF1 is rare and has only been reported in 16 case reports to date [3].

In patients with NF1, the risk of developing pheochromocytoma is 10 times higher than in the general population, with a prevalence ranging from 1 to 15% depending on the study [2]. The average age at diagnosis is around 40 years, and the tumor is most often unilateral (60-80%) and non-metastatic (>90%) [2]. In addition, the size of pheochromocytomas reported in patients with NF1 is significantly smaller than in other patients (2.75 cm vs. 5.90 cm) [3].

Kimura et al. [5] suggested that the loss of neurofibromin due to the NF1 mutation may lead to abnormal proliferation of Schwann cells, resulting in marked proliferation of chromaffin cells, which in turn cause pheochromocytoma.

The diagnosis is suspected when clinical signs of hypertensive episodes (sweating, palpitations, headaches, anxiety, agitation) or classically fluctuating and/or treatment-resistant hypertension are present, and is based on plasma and/or urinary metanephrine levels and abdominal imaging [2]. Its management is not specific to NF1 and is based on surgical treatment in combination with alpha and beta blockers prior to surgery.

The risk of GIST, mesenchymal tumors of the digestive tract derived from Cajal cells or one of their precursors, is 150 times higher in patients with NF1 than in the general population, with a prevalence of 6-7% [3] [2]. Gorgel et al [6] have stated that activation of the RAS proto-oncogene pathway in patients with NF1 leads to the proliferation of Cajal cells and the development of GISTs. GISTs associated with NF1 occur at an early age, are often multiple, frequently located in the small intestine, and do not usually harbor KIT and PDGFRA mutations, which are generally associated with sporadic GISTs[2]. The majority of patients with GIST, estimated at around 80%, present with clinical signs such as abdominal pain, a palpable abdominal mass, gastrointestinal bleeding, or intestinal obstruction. [8] Compared to sporadic forms, GISTs occurring in the context of NF1 are most often multiple, preferentially located in the small intestine, and frequently detected incidentally. From a histological point of view, they are distinguished by a predominance of fusiform morphology and higher expression of CD34. [9]

Diagnosis is based on endoscopic examination of the digestive tract, and treatment involves complete surgical resection with tyrosine kinase receptor inhibitor therapy in cases of high-risk lesions [1].

The simultaneous occurrence of pheochromocytoma and GIST in patients with neurofibromatosis type 1 is extremely rare. Several case reports in the literature have highlighted this co-occurrence, emphasizing the importance of systematic monitoring in these patients. Other case reports and literature reviews confirm this unusual combination, sometimes in the presence of multiple or bilateral tumors [6] [10]. In addition, a systematically evaluated cohort study of 108 NF1 patients showed a high prevalence of pheochromocytomas and a significant incidence of GISTs, although both remain rare, illustrating the importance of close clinical and radiological monitoring in these patients [10].

Conclusion

Although the co-occurrence of pheochromocytoma and GIST in NF1 is considered unusual and rare, patients with NF1 who have hypertension and gastrointestinal symptoms should be rigorously screened for both pheochromocytoma and GIST. In addition, regular lifelong post-treatment follow-up for both types of tumors should be maintained in these patients in order to detect any recurrence.

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