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*RESEARCH ARTICLE*

# SYNCHRONOUS GASTROINTESTINAL STROMAL TUMOR AND PHEOCHROMOCYTOMA IN A PATIENT WITH NEUROFIBROMATOSIS TYPE 1:A CASE REPORT

**Malak Bennani[1], Mouna Darfaoui[1], Fatima Ezzahra Hazmiri[2], Fatima Ezzahra Ghlalou[2], Hanane Rais[2], Abdelhamid El Omrani[1] and Mouna Khouchani[1]**

1. Radiation Oncology Department, Mohamed VI Teaching Hospital, Marrakech, Morocco.
2. Anatomical Pathology Department, Mohamed VI Teaching Hospital, Marrakech, Morocco.

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## *Abstract*

The risk of tumours including pheochromocytoma and gastrointestinal stromal tumour (GIST) has been reported to be higher in neurofibromatosis type 1 (NF1) patients.The co-occurrence of pheochromocytoma and GIST among NF1 patients is rare. In this case report, we describe the case of a sixty-five-year- old woman who presented with abdominal pain. CT imaging revealed two abdominal masses. The patient underwent surgical treatment with no complications and after one year remains in oncological remission. The pheochromocytoma and GIST tumours were diagnosed based on pathology. Here, we discuss the rare association of pheochromocytoma and GIST and the asymptomatic presentation of those tumours in an NF1 patient. We further suggest that in NF1 patients a high level of vigilance can help making early diagnosis.



## Introduction:-

Neurofibromatosis type 1 (NF1) or Recklinghausen disease is a hereditary cancer predisposition syndrome characterized by its neurologic, dermatologic and orthopedic manifestations. It is developing from loss of function of the NF1 gene product, the tumor-suppressor protein neurofibromin (1).

There is a spectrum of tumors that affects individuals with NF1 at an increased incidence as compared to the general population(2). In addition to the NF1-distinguishing neoplasms, such as neurofibromas, malignant peripheral nerve sheath tumors and gliomas, there has been a growing number of literatures reporting an association between NF1 and gastrointestinal stromal tumors (GIST). Although it is a relatively rare entity, occurring at an incidence of 6 to 15 per one million, GIST is the most common mesenchymal tumor of the gastrointestinal tract (3).The co-occurrence of pheochromocytoma and GIST among NF1 patients is rare, with only approximately 16 documented cases reported in the English language to date (3).

We herein report a case of an NF1 patient with that uncommon clinical presentation: simultaneous occurrence of GIST and pheochromocytoma.

**Casereport:**
A sixty-five-year- old Moroccanwomanwith clinical diagnosis of neurofibromatosis presented to the hospital with chronic abdominal pain.

**Corresponding Author:- Malak Bennani**
Address:- Radiation Oncology Department, Mohamed VI Teaching Hospital, Marrakech, Morocco.

Except for the multiple café -au-lait spots and cutaneous neurofibromas, physical examination results were unremarkable.

Her blood pressure was 130/86 mm Hg and pulse rate was 74 beats/min. She also lacked the typical symptoms of catecholamine excess.

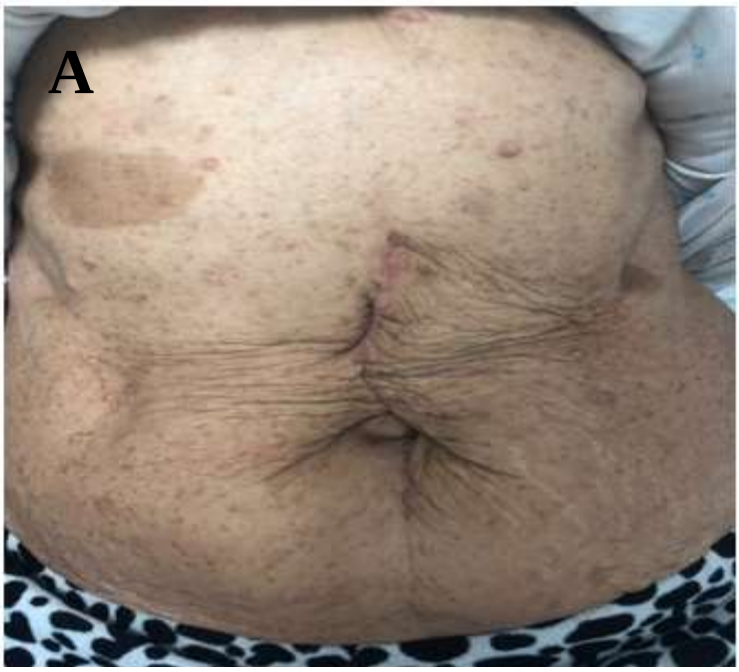
CT imaging was performed and revealed two abdominal masses. The first one is under pancreatic (44x58 mm), in contact with the crus of diaphragm, abdominal aorta, left renal pedicle and splenic pedicle. The second one is located in the left flank (20x27mm) and is in intimate contact with the small intestines.

The patient underwent surgery. Surgical exploration found a retroperitoneal mass of 6x5 cm, hypervascularized with hemorrhagic content, adherent to the spleen and pancreas without invading them. The second mass measures 3x3 cm, with extra and intra luminal development in the first jejunal loop. Both masses were resected.

Histopathological examinations demonstrated that the two tumors had different origins. The retroperitoneal tumor showed histologic features of pheochromocytoma with chromogranin, S100 and synaptophysine positive cells. whereas CD117 staining was negative.

Microscopic and immunohistochemical examination of the jejunal tumor confirmed low risk GIST with expression of both Dog 1 and CD117, Ki-67 stain indicating approximately 10% immunoreactivity.

No adjuvant therapy was indicated for this patient. A CT-scan was performed every three months, showing no sign of recurrence one year after.



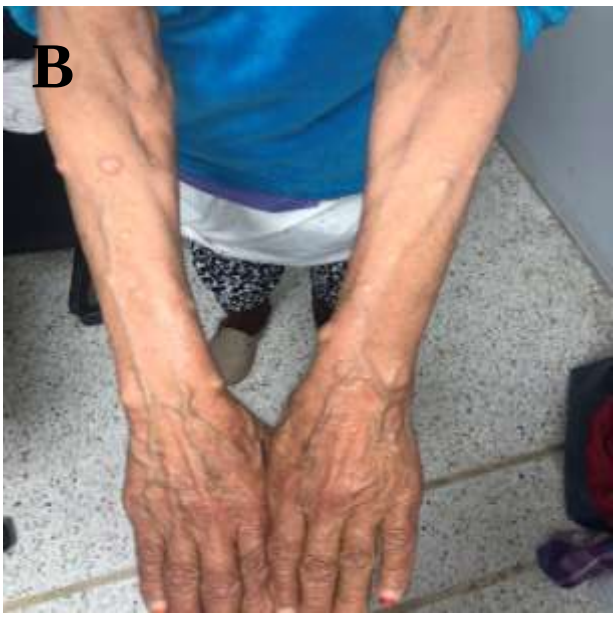



**Figure 1:-** Clinical photograph of the patient(A) Cafe au lait spots (B) Multiple neurofibromas.

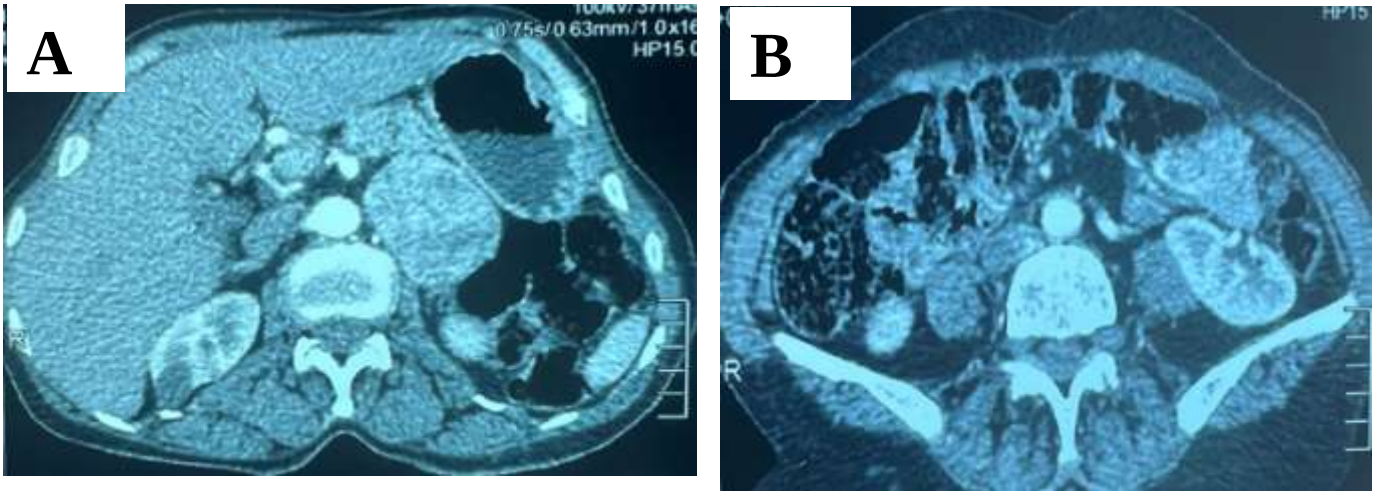



**Figure 2**:- Abdominal CT (A) Mass of44x58 mm, in contact with the crus of diaphragm, abdominal aorta, left renal pedicle and splenic pedicle.(B) Left flank mass (20x27mm)in intimate contact with the small intestines.

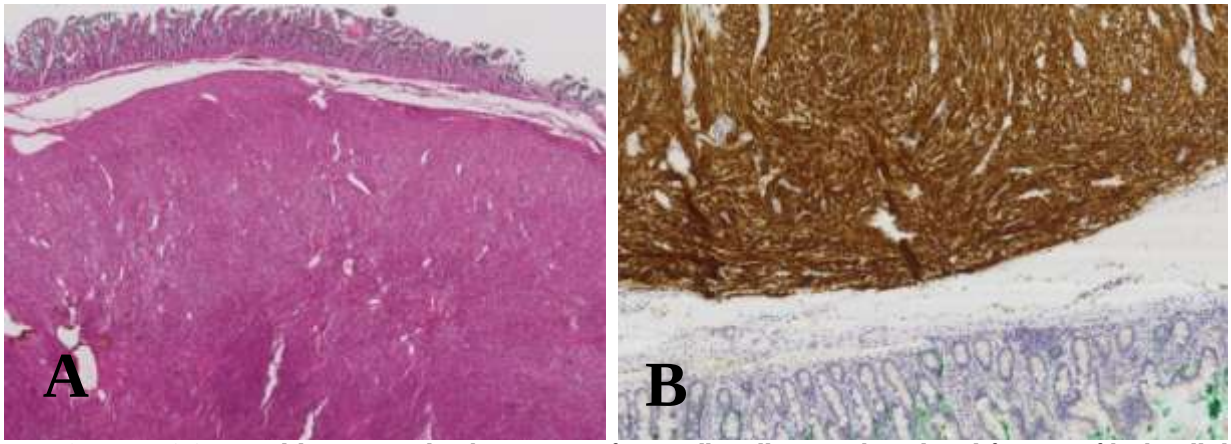



**Figure3:-** (A) Jejunal location under the mucosa of a spindle-cell mesenchymal proliferation of high cell density;

extended to the muscularis and serosa in favor of a Gastrointsetinal stromal tumor. (B) Intense and diffuse membrane and cytoplasmic expression of tumor cells of the anti-Dog1 antibody.

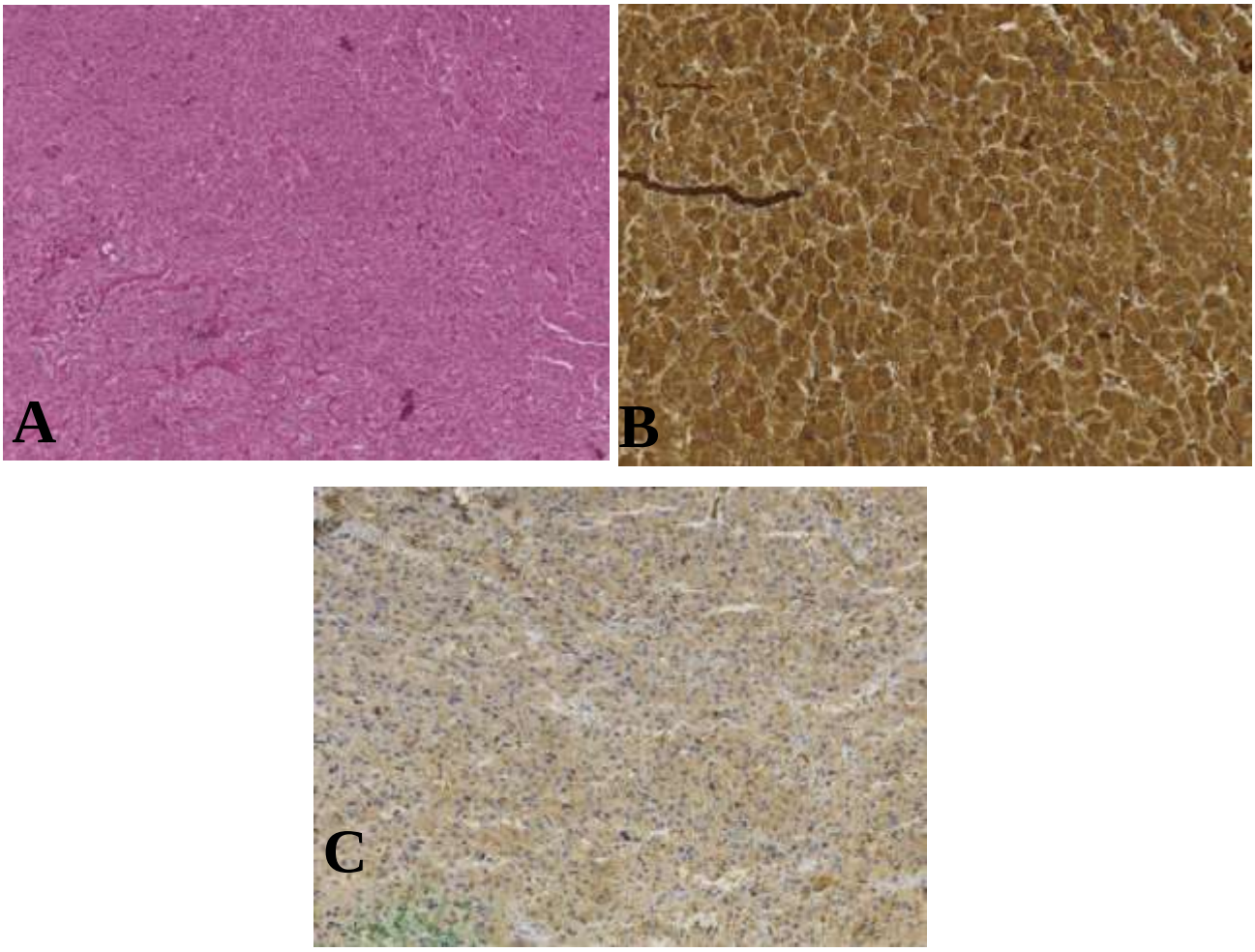



**Figure 4:- (**A) Tumor proliferation of endocrine differentiation arranged in large nests with a mitotic index of 2 mitoses/10 without atypical mitoses or necrosis.
(B) Moderate and diffuse granular cytoplasmic expression of anti-Chromogranin antibody tumor cells. (C) Moderate cytoplasmic expression of anti-Synaptophysin antibody in tumor cells.

## Discussion:-

NF1 is mostly characterized as a neurocutaneous disorder, with both café au lait patches and cutaneous neurofibromas occurring at frequencies greater than 99% (4).

It is one of the most common autosomal dominant conditions in which affected individuals have an increased risk of malignancy. Patients with NF1 harbor an increased risk for developing both benign and malignant tumors. Indeed, NF1 patients have 2.7-fold increased cancer risk with a cumulative risk of 20% in affected patients over 50 years old. The incidence of malignancy varies between 4% and 52% in NF1 patients.Malignant peripheral nerve sheath tumors are the most common malignant tumors observed in NF1 patients. Other malignant tumors strongly associated with NF1 patients include rhabdomyosarcoma, gastrointestinal stromal tumors, neuroectodermaltumors,pheochromocytomas, and breast carcinoma(2).

The genetic basis of this disease is a mutation in the NF1 gene located on chromosome 17q11.2. NF1 encodes neurofibromin, a tumor suppressor protein. Neurofibromin regulates cellular proliferation via inactivation of RAS, a protein that stimulates signal transduction through the MAP-kinase pathway when activated. The resultant loss of function of neurofibromin predisposes to the development of benign and malignant tumors(5).

Pheochromocytoma is a catecholamine secreting tumorthat arises from the chromaffin cells of the sympathoadrenal system. Most pheochromocytomas are sporadic but 10%–15% are hereditary in diseases such as NF1, multiple endocrine neoplasia type 2, von Hippel-Lindaudisease and familial carotid body tumours(6).The incidence of pheochromocytoma in normotensive patients with NF1 is 1%–5.7%(7).In hypertensive NF1 patients, the rate increases to 20%–50%(8).

Almost 80% of NF1 patients with pheochromocytoma have suggestive symptoms, for example, tachycardia, hypertension and palpitations(9). In addition, the reported size of pheochromocytomas in NF1 patients is significantly smaller than in non- NF1 patients (2.75 cm vs 5.90 cm) due to earlier screening and incidental discovery of tumours in NF1 patients(10).In the present case, the patient had no obvious clinical symptoms of pheochromocytoma, including hypertension, and the tumour was larger than that reported in the previously cited study. It could be presumed that this casehad a late tumour identification.

Gastrointestinal stromal tumors (GISTs) are the most common nonepithelial tumors of the gastrointestinal tract, accounting for 1%–3% of all gastrointestinal malignancies(11). GISTs can arise from any part of the gastrointestinal tract. However, the most commonly affected site in NF1 patients is the small intestine compared with the stomach in the general population (12).

Patients with NF1 are at 45-fold increased risk of developing GISTs compared with normal controls. The incidence of GIST in NF1 patients is 3.9%–25% compared with 10–13 per 100,000 in the general population. Most notably, the prevalence of NF1 in patients with GIST is up to 6%(13).

The most frequent signs and symptoms of gastro-intestinal stromal tumors are abdominal pain, abdominal mass, gastrointestinal hemorrhage, and bowel obstruction or perforation.

Surgical removal is the definitive therapy for pheochromocytoma and was performed in the present case. Following surgery, lifelong surveillance for recurrent of pheochromocytoma should be conducted (14).Regarding GIST, about 60% of patients are cured with surgery alone, particularly those with low-to-moderate risk GIST, such as our patient. In those with high-risk GIST, in addition to surgery, imatinib mesylate should be prescribed to suppress CD117 receptors and thus to prevent tumour recurrence or metastasis(15).

The combination of these two tumours without a background of NF1 had been described as Carney- Stratakis dyad. However, in this dyad, most of the patients had paraganglioma rather than pheochromocytoma, which was not the situation in our case. Possible theories regarding this rare association have been proposed in multiple studies. For example, Kimura et al suggested that the loss of neurofibromin due to the NF1 mutation can lead to abnormal proliferation of Schwann cells resulting in marked proliferation of chromaffin cells which, in turn, causes pheochromocytoma(16). Georges et al stated that the activation of the RAS proto-oncogene pathway in NF1 patients causes Cajal cell proliferation, resulting in GIST development(17). This causal relationship was confirmed through identification of somatic NF1 mutations in interstitial cells of Cajal in the gastrointestinal tract.(18)

## Conclusion:-

The current study reiterates that cases of NF1 occurring with pheochromocytoma and GIST are rare. This combination should be considered in all patients with NFI presenting with an abdominal mass and with or without symptoms suggestive of pheochromocytoma.Therefore, apheochromocytoma should be excluded before a patient with neurofibromatosis I undergoes surgery for a gastrointestinal stromal tumor because an undiagnosed pheochromocytoma carries a high risk of life-threatening cardiovascularcomplications during surgery.

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