Pancreatic Atypical Neurofibromatous Neoplasm with Uncertain Biological Potential (ANNUBP) Mimicking a Solid Pseudopapillary Tumor Pancreatic ANNUBP

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Summary

Atypical neurofibromatous neoplasms of uncertain biological potential have recently been added as a subset of lesions that have the potential to transform into malignant peripheral nerve sheath tumors in patients with neurofibromatosis type 1. Only a few cases of atypical neurofibromatous neoplasms of uncertain biological potential , have been reported in the literature. Here we present the first case of this type of neoplasm located in the pancreas in a 30-year-old woman with neurofibromatosis type 1. The mass was discovered incidentally on imaging studies. Computed tomography and magnetic resonance imaging showed a 3 x 2 cm solid-cystic mass in the head of the pancreas, suggestive of a pseudopapillary solid tumor. Following an inconclusive endoscopic ultrasound-guided biopsy, a pancreaticoduodenectomy was performed. The patient had an uneventful postoperative recovery. Histopathological and immunohistochemical analysis confirmed the diagnosis of atypical neurofibromatous neoplasms of uncertain biological potential. To our knowledge, this is the first report of this type of tumor located in the pancreas. They are often difficult to differentiate from other solid and solid-cystic tumors of the pancreas based on imaging studies. Imaging techniques such as magnetic resonance imaging and positron emission tomography along with computed tomography, combined with histopathology, and a history of type 1 neurofibromatosis are essential for an accurate diagnosis. Current treatment consists of radical surgical removal of the tumor, due to the risk of malignant transformation. This case highlights the importance of considering atypical neurofibromatous neoplasms of uncertain biological potential as a differential diagnosis in patients with neurofibromatosis type 1 and a pancreatic mass. Fur-

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ther studies are needed to improve preoperative diagnostic strategies and evaluate long-term prognosis after surgical resection.

Keywords. *Atypical neurofibromatous neoplasms of uncertain biological potential, pancreatic tumor, pancreaticoduodenectomy, neurofibromatosis type 1.*

Neoplasia neurofibromatosa atípica pancreática con potencial biológico incierto (ANNUBP) simulando un tumor pseudopapilar sólido pancreático

Resumen

Las neoplasias neurofibromatosas atípicas de potencial biológico incierto se han añadido recientemente como un subconjunto de lesiones con potencial de transformación en tumores malignos de la vaina del nervio periférico en pacientes con neurofibromatosis tipo 1. Solo se han reportado unos pocos casos de neoplasias neurofibromatosas atípicas de potencial biológico incierto en la literatura. Aquí presentamos el primer caso de este tipo de neoplasia localizada en páncreas en una mujer de 30 años con neurofibromatosis tipo 1. La masa fue descubierta incidentalmente en estudios de imagen. La tomografía computarizada y la resonancia magnética mostraron una masa sólido-quística de 3 x 2 cm en la cabeza del páncreas, sugestiva de un tumor sólido pseudopapilar. Tras una biopsia guiada por ultrasonido endoscópico no concluyente, se realizó una duodenopancreatectomía. La paciente tuvo una recuperación postoperatoria sin complicaciones. El análisis histopatológico e inmunohistoquímico confirmó el diagnóstico de neoplasia neurofibromatosa atípica de potencial biológico incierto. Hasta donde sabemos, este es el primer informe sobre este tipo de tumor localizado en el páncreas. Suelen ser difíciles de diferenciar de otros tumores sólidos y sólido-quísticos del páncreas mediante estudios de imagen. Técnicas de imagen como la resonancia magnética y la tomografía por emisión de positrones junto con la tomografía computarizada, combinadas con la histopatología y los antecedentes de neurofibromatosis tipo 1 son esenciales para un diagnóstico preciso. El tratamiento actual consiste en la extirpación quirúrgica radical del tumor debido al riesgo de transformación maligna. Este caso resalta la importancia de considerar las neoplasias neurofibromatosas atípicas de potencial biológico incierto como diagnóstico diferencial en aquellos pacientes con neurofibromatosis tipo 1 y una masa pancreática. Se requieren más estudios para mejorar las estrategias diagnósticas preoperatorias y evaluar el pronóstico a largo plazo tras la resección quirúrgica.

Palabras claves. *Neoplasias neurofibromatosas atípicas de potencial biológico incierto, tumor pancreático, pancreaticoduodenectomía, neurofibromatosis tipo 1.*

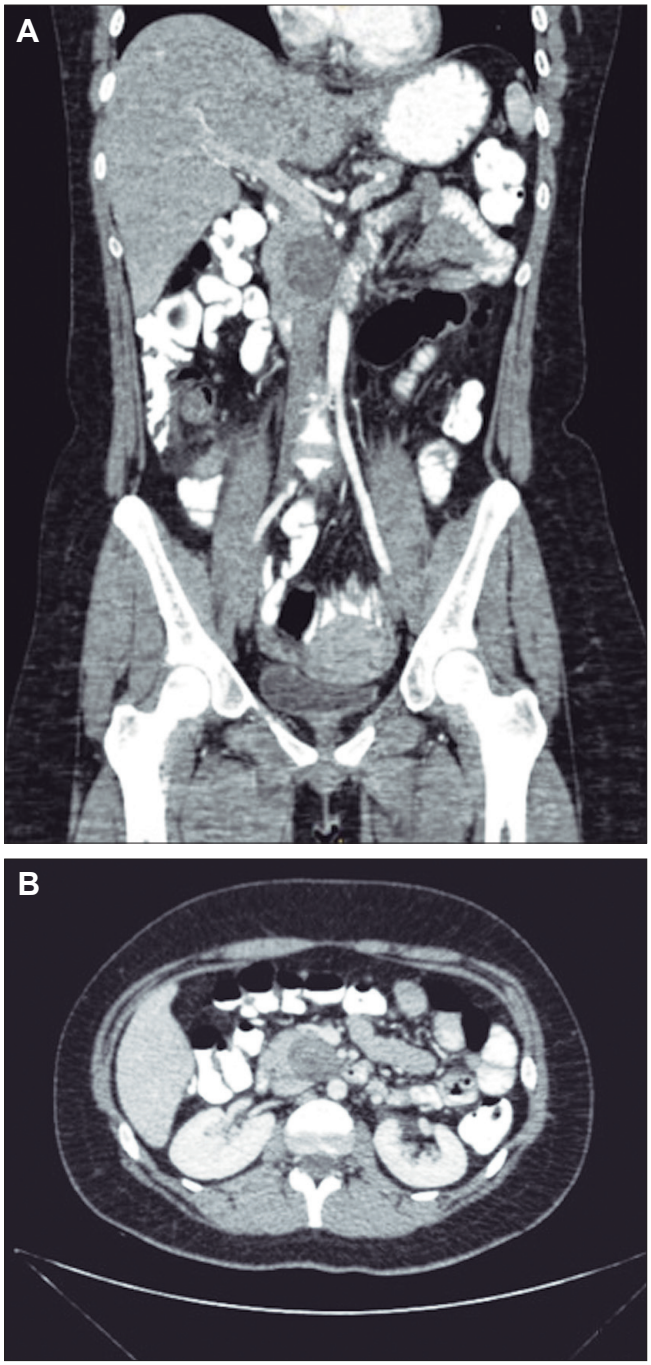
Introducción

Neurofibromatosis type 1 (NF-1) is an autosomal dominant disorder with an estimated incidence of approximately 1 in 3,000 people, though this varyies by region.[1] Patients with NF-1 are highly predisposed to develop benign and malignant tumors that affect the central and peripheral nervous systems. Although most NF-1 manifestations impact the nervous system, other organs and tissues may also be affected.[2-7] Among patients who develop neurofibromas, 8 - 15% may develop a malignant peripheral nerve sheath tumor (MPNST) during their lifetime.[8] MPNSTs usually originate from a plexiform neurofibroma (PN) or an atypical neurofibromatous neoplasm of unknown biological potential (ANNUBP). Both PNs an ANNUBPs are considered premalignant lesions.[9]

Case report

A 30-year-old female patient with a history of NF-1 was diagnosed incidentally with a 3 x 2 cm lesion in the pancreatic head (uncinate process) during a CT scan that was ordered to rule out acute appendicitis. The CT scan showed a 3 x 3 cm hypodense solid lesion in the pancreatic head that exhibited mild, slightly heterogeneous, and progressive enhancement after contrast was administered. These findings were suggestive of a solid pseudopapillary neoplasm. (Figure 1). The patient underwent surgery for acute appendicitis, after which the pancreatic mass was further investigated. Routine laboratory tests and tumor markers (CA 19-9, CEA, and chromogranin A) were within normal limits. An MRI revealed a 38 x 29 mm ovoid lesion with smooth contours and clearly defined margins. The tumor displayed heterogeneous signal characteristics, including moderate hyperintensity on T1-weighted images and hypointensity on T2-weighted images. Diffusion-weighted sequences revealed increased signal restriction. Post-contrast imaging demonstrated moderate, progressive enhancement with a non-uniform pattern, consistent with areas of cystic degeneration. The lesion did not cause ductal dilation or invasion of blood vessels. (Figure 2).

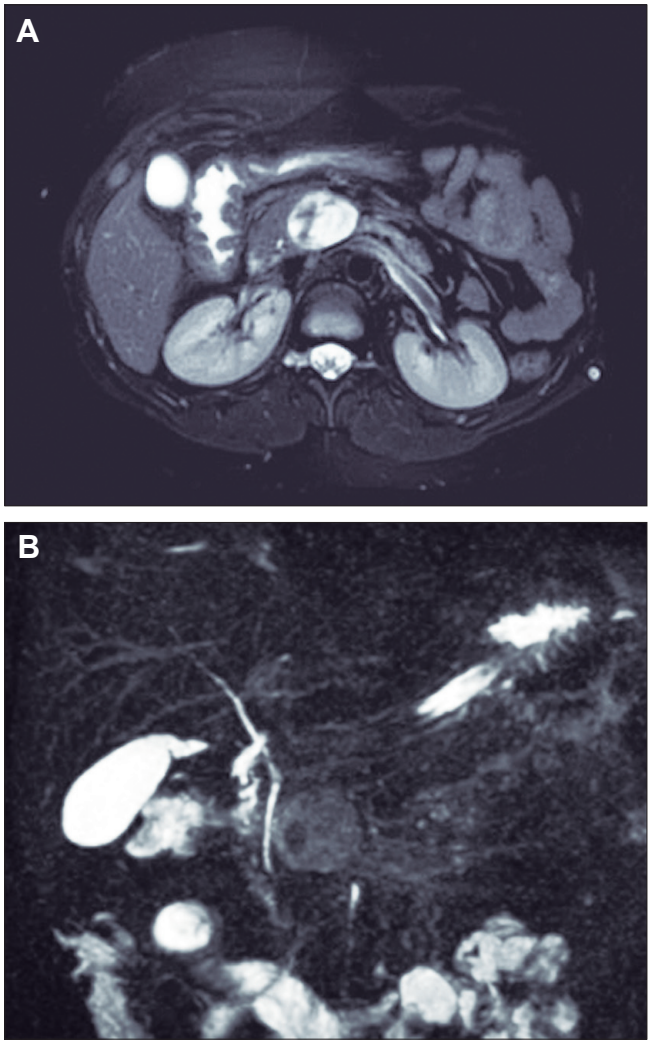
Figure 1. *CT Scan showing a 3 x 3 cm hypodense solid lesion located at the junction of the pancreatic head and the uncinate process*



The lesion demonstrated mild, slightly heterogeneous, progressive enhancement following contrast administration. Image (A) depicts a coronal section and image (B) represents an axial section.

An endoscopic ultrasound was performed, showing a 3.5 cm solid-cystic lesion in the pancreatic uncinate process that displaced the superior mesenteric vein without signs of invasion. A biopsy was taken, but the pathology report was inconclusive. The chest CT was normal. The patient underwent a conventional pancreaticoduodenectomy with single-loop reconstruction. The postoperative course was uneventful, and the patient was discharged on the 12th postoperative day.

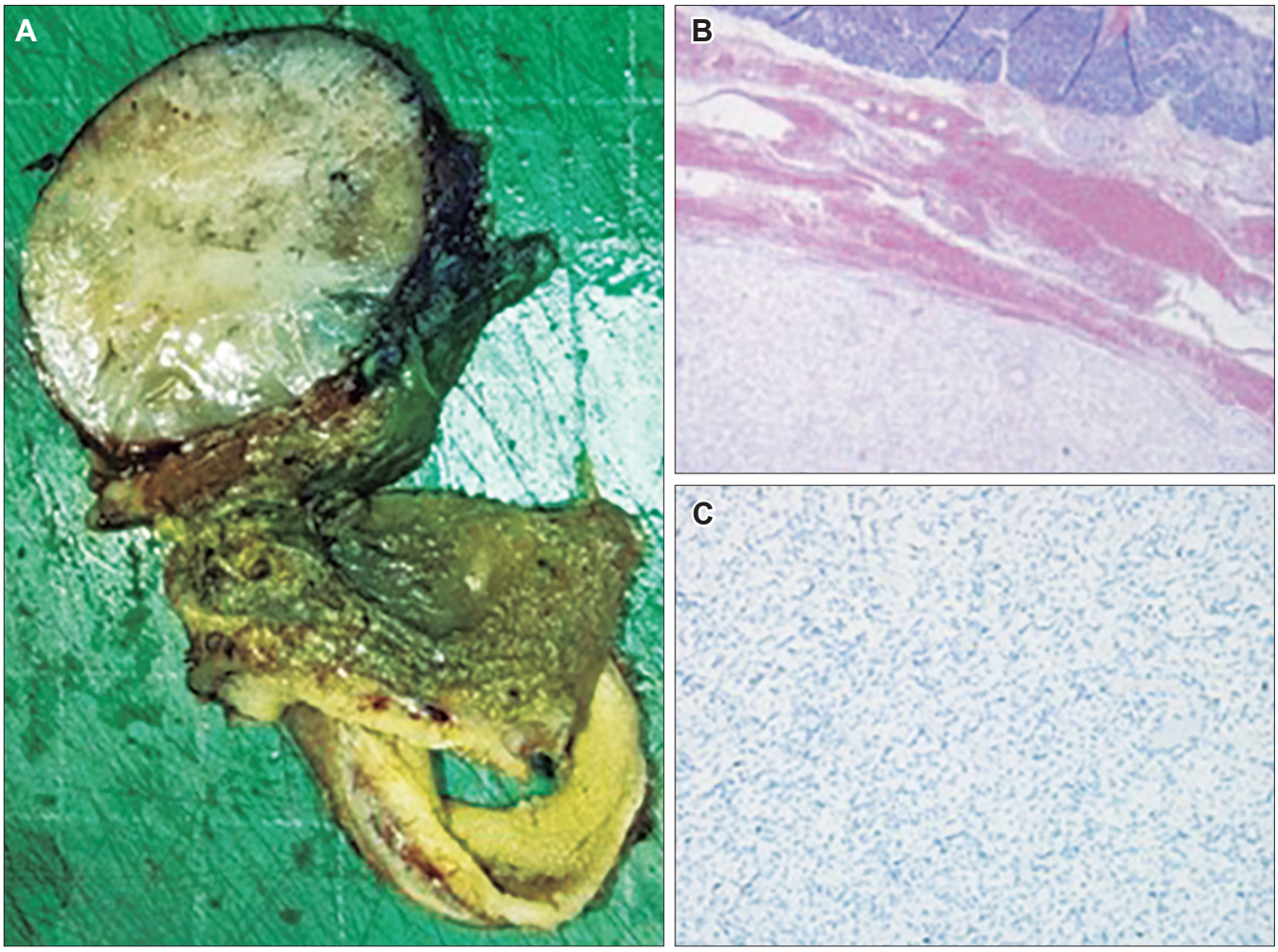
Figure 2. *MRI imaging showing an ovoid lesion with smooth contours and clearly defined margins*



The lesion displayed heterogeneous signal characteristics, demonstrating moderate hyperintensity on T1 and hypointensity on T2. Post-contrast imaging revealed moderate, progressive enhancement with a non-uniform pattern consistent with areas of cystic degeneration (A). Image (B) depicts the magnetic resonance cholangiopancreatography.

Histopathology showed a 3.2 x 3 cm neurofibromatous lesion with fusocellular proliferation, areas of nuclear atypia, and hypercellularity. None of the 19 harvested lymph nodes were positive. Immunohistochemistry analysis confirmed the ANNUBP diagnosis (SOX10: diffuse positive; S100: diffuse positive; P53: > 10% mutated cells; P16: preserved nuclear expression; Ki67: 2% - low proliferative index). (Figure 3).

Figure 3. *Surgical specimen: Nodular lesion with a greyish colour, well-defined margins, measuring 3.2 x 3 cm*



(**3-A**). Histopathology: Lesion with a neurofibromatous appearance showing areas of nuclear atypia and hypercellularity in the absence of mitosis and necrosis (**3-B** -H&E- and **3-C** -IHC p53-).

Discussion

NF-1 is the most common neurocutaneous disorder, affecting approximately one in 3,000 individuals. Typical diagnostic features include café-au-lait macules in the axillary or inguinal regions, freckles, and plexiform neurofibromas (PNs). Neurofibromas originate in the peripheral nerve sheath and are more frequently located in the skin and subcutaneous tissue of the head, neck, trunk, and extremities. Sometimes, however, they are located deeper within the muscle or spinal nerve roots.[9]

ANNUBPs are borderline tumors representing an intermediate stage of malignant peripheral nerve sheath tumors (MPNSTs). MPNSTs are highly aggressive soft tissue sarcomas with a 5-year survival rate of 20% to 50%.[10] Previous studies have demonstrated that NF1-associated MPNSTs often originate from PN or ANNUBPs, both classified as precancerous lesions.[9] It is estimated that eight to 15% of patients with these lesions may progress to MPNSTs during their lifetime.[11,1,12-13] NF1 and previous radiation exposure have been identified as risk factors for developing MPNSTs. PN and ANNUBP are novel concepts of premalignant MPNST lesions, with sequential mutations leading to sarcoma development. Rapid neurofibroma growth should prompt exhaustive evaluation to rule out malignant transformation.[1]

The term ANNUBP was first proposed in 2017 during a consensus meeting.[9] It was determined that tumors containing at least two of the following features -nuclear atypia, loss of neurofibroma architecture, high cellularity, and/or mitotic activity > 1/50 but < 3/10 high power fields- had a lower risk of local recurrence and metastases[8] when compared to MPNST, and should be classified as

ANNUBP. This novel categorization avoids aggressive and morbid therapy in tumors with borderline malignant behaviour. Therefore, the term "low-grade MPNST" should be discouraged, unless clear histological features of malignancy are present, such as the typical histopathological appearance of a sarcoma with necrosis and a high mitotic index (more than three in 10 high-power fields).[8]

Neurofibromatous lesions rarely affect the lungs, abdominal or retroperitoneal organs. There are few reports on pancreatic neurofibromatous lesions in the literature.[11, 3-5, 14-16] However, none of them were categorized as ANNUBP. On a CT scan, pancreatic neurofibromas appear as well-circumscribed, hypoattenuating masses, or mildly enhancing masses. The classic appearance of an MRI is a "target" with a T2 hypointense core surrounded by a T2 hyperintense ring, similar to neurofibromas elsewhere in the body.[17]

Kodai Miyamoto *et al.* reported the case of a 19-year-old male with an incidentally discovered mediastinal lesion. An MRI showed a well-defined, T1-isointense and T2-hyperintense mass without associated tumor necrosis. FDG-PET/CT revealed hypermetabolism in the tumor's central region. A preoperative CT-guided biopsy confirmed ANNUBP diagnosis, and the patient underwent surgery with clear margins. At one-year follow-up, no recurrence were observed.[18]

Interestingly, ANNUBP may exhibit increased FDG uptake on PET/CT. Some studies have reported that FDG-PET/CT is a useful tool for differenting MPNSTs from neurofibromas in NF1 patients, establishing a maximum standard uptake value (SUV) cutoff between 3.5 and 7.48. Malignancy is generally considered absent if the SUV is below 2.5, and MPNST is suspected when the SUV exceeds 3.5. However, other studies suggest that SUV values above 4.0 or 6.1 offer greater specificity in diagnosing MPNSTs. Due to the poor prognosis of MPNSTs, the 3.5 SUVmax cutoff is widely used. Furthermore, PET/CT may help detect occult metastases.[4] MRI may also help differentiate MPNSTs from neurofibromas or premalignant lesions. Tumor size > 64mm, a peripheral enhancement pattern, perilesional edema, and intratumoral cystic changes are considered worrisome features.[19]

Differential diagnoses to consider include gastrointestinal stromal tumors (GISTs), pancreatic neuroendocrine tumors (PNETs), solid pseudopapillary tumors, and pancreatic adenocarcinomas.[20] Similarly to pancreatic ANNUBPs, GISTs may show FDG uptake on PET/CT and can exhibit hypercellularity/cellular atypia on histopathology.[21] PNETs also represent an important differential diagnosis, affecting 10% of patients with NF-1. They usually appear as well-defined masses with an intense gadolinium uptake, which helps differentiate them from an ANNUBP.[22] Pancreatic lymphoma, though rare, can also present as a pancreatic mass with elevated FDG uptake on PET/CT. In this setting, a detailed clinical evaluation, high-quality cross-sectional imaging, tumor markers, histopathology, and immunohistochemistry are of the utmost importance for an accurate diagnosis.[7-10]

Currently, surgery is the preferred treatment for ANNUBP. Radical resection with negative margins may avoid malignant transformation. The role of chemotherapy in the treatment of this type of tumors is still being investigated.[23-26] Furthermore, the prognosis for patients with resected ANNUBP remains unclear due to the lack of long-term follow-up data.

Conclusions

AANUBP should be considered in the differential diagnosis of patients with NF-1 who present with a pancreatic mass. Further studies are needed to improve non-invasive preoperative diagnostic tools, determine risk factors for malignant transformation, and evaluate long-term outcomes following resection.

Ethical Approval and Patient Consent. *Written informed consent was obtained from the patient for participation and publication of this case. The study was approved by the Institutional Ethics Committee of our hospital.*

Intellectual Property. *The authors declare that the data and figures presented in the manuscript are original and were carried out at their belonging institution.*

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