Clinical report

Nasal mucosa: A new site for tissue biopsy to diagnose hereditary TTR amyloidosis

Miguel Munar-Qués a,*, Manel Solé b, Jacinto Martínez-Nadal c, Antonio Murcia-Sáiz d, José Manuel Mas-Degano e

a Grupo de Estudio de la PAF, Majorca, Spain
b Servicio de Anatomía Patológica, Hospital Clinic, Universidad de Barcelona, Barcelona, Spain
c Servicio de Otorrinolaringología, Hospital Universitario Son Espases, Majorca, Spain
d Servicio de Otorrinolaringología, Clínica Rotger, Majorca, Spain
e Servicio de Anatomía Patológica, Clínica Rotger, Majorca, Spain

ABSTRACT

Background and objective: We report 2 carriers of the TTRV30M mutation and its plasmatic biochemical marker with clinical symptoms compatible with hereditary TTR amyloidosis.

Materials and methods: Based on our previously reported casual finding of amyloid TTR in nasal mucosa (2008), we requested biopsy of this tissue to search for amyloid with Congo red staining and TTR immunohistochemical analysis.

Results: The histological diagnosis was achieved by retrospective analysis of surgical sinonasal biopsy in the first patient and prospective biopsy of inferior nasal concha in the second. Large interstitial deposits of ATTR were observed in both cases.

Conclusions: We suggest nasal mucosa as a suitable site for tissue biopsy in patients with suspected hereditary TTR amyloidosis.

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Mucosa nasal: un nuevo tejido para el diagnóstico biópsico de amiloidosis hereditaria relacionada con transtirretina

RESUMEN

Antecedentes y objetivo: Presentamos 2 portadores de la mutación TTRV30M y su marcador bioquímico plasmático, con síntomas sugestivos de amiloidosis hereditaria TTR.

Material y métodos: Basándonos en el hallazgo casual de amiloide TTR en la mucosa nasal previamente publicado (2008), indicamos la biopsia de este tejido para la búsqueda de amiloide TTR con tinción Rojo Congo y análisis inmunohistoquímico de TTR.

Resultados: El diagnóstico histológico se logró en el primer enfermo con análisis retrospectivo de la biopsia de material operatorio sinonasal, y en el segundo con biopsia prospectiva del cornete nasal inferior. En ambos casos se observaron grandes depósitos intersticiales de amiloide de amiloidosis hereditaria relacionada con transtirretina.

Conclusiones: Consideramos que la biopsia de la mucosa nasal es idónea para el diagnóstico de pacientes con sospecha de amiloidosis hereditaria TTR.

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INTRODUCTION

In 1952, Corino Andrade first described systemic hereditary amyloidosis, named familial amyloid polyneuropathy (FAP). Although this term is still accepted today, the disorder is more
commonly referred to as hereditary TTR amyloidosis. This entity is characterized by distal sensorimotor polyneuropathy in lower limbs, autonomic disturbances, autosomal dominant heredity and fatal outcome within approximately 10 years. The disorder has received considerable attention since it was first described and it is no longer considered a rare disease. For this reason, much is known about FAP.\(^{2,4}\)

Diagnostic techniques for FAP have changed over the years, and have been based on histological, molecular, and tissue typing methods. Histological diagnosis consists of prospective biopsy of nerves or other tissues. Since 1972 retrospective analyses of biopsies have also been performed in living or deceased relatives of probands.\(^5\) Tissues most widely used today in histological analysis are skin, subcutaneous abdominal fat, rectal mucosa and labial salivary glands.\(^6,7\) Molecular diagnosis includes genomic and proteomic analysis. This method identifies the mutation of the TTR variant and the TTR plasmatic variant which is the biochemical marker of the mutation. Amyloid typing is performed by immunohistochemical analysis (IHC), which helps to determine the type of FAP amyloid (ATTR) and those of other most frequent systemic amyloidosis, hence being particularly useful for the differential diagnosis.

In 2008 we reported\(^8\) the casual and surprising finding of ATTR in nasal mucosa of inferior nasal concha in a female FAP patient who had undergone LTX 4 years ago. We concluded that if inferior nasal concha was a frequent location of amyloid in FAP, it could be an optimal biopsy site. For this reason, since that year we included the nasal mucosa biopsy in our protocol to prove the frequency and degree of deposits. The possibility to search ATTR happened in 2012 when we visited 2 patients with suspected hereditary TTR amyloidosis, which are reported in this paper.

**Patients and methods**

**Case 1.** In June 2012, a 49-year-old male carrier of the TTR30M mutation and its plasmatic biochemical marker was visited for suspected familial amyloidosis.

**Antecedents.** Since the age of 14, he had episodes of sinusitis and asthma. At 48 years he had breathing difficulties due to a blocked nose. Rhinosinusal CT scan showed left septal deviation, right concha bullosa, marked inflammation with secretion and polyposis in ethmoidal sinuses, and less inflammation in the other sinuses. Vast endoscopic rhinosinusal surgery, septoplasty and radiofrequency for the right turbinate hypertrophy, were performed. HE staining showed hyperplastic mucosa and inflammatory nasal polyps. After surgery, breathing progressively returned to normal and asthma improved.

**Present problem.** At age 47, he developed progressive sexual dysfunction; one-year later he presented mild difficulty in walking and slight orthostatic hypotension. Due to these symptoms and his condition of carrier, hereditary TTR amyloidosis (FAP) was suspected although neurological examination of lower limbs was normal. The suspected diagnosis was supported by heart rate variability\(^9\) and an electrophysiological study with chronic sensorimotor polyneuropathy that was predominantly axonal. To identify amyloid in the nasal mucosa we analyzed the aforementioned operative biopsy with CR staining and TTR IHC.

**Case 2.** A 29-year-old woman, also a carrier of the TTR30M mutation and its plasmatic biochemical marker, was screened for the familial disease. She complained of digestive disturbances, first appearing six months earlier. These included slight gastric repletion and bouts of diarrhea every 2–3 days. The frequency of bouts was progressive, with encopresis on three occasions. A colonoscopy showed no inflammatory or neoplastic findings; rectal mucosa biopsy stained with HE was normal. We suspected FAP although a neurological examination of the lower limbs and an electrophysiological study were normal. Diagnosis was supported by disturbances of HRV.\(^9\) To search amyloid we investigated the cited biopsy of rectal mucosa with CR stain, which was negative. Based on our publication,\(^8\) we referred the patient to the ENT for biopsy of inferior nasal concha. Anterior rhinoscopy showed a non-deviated septum, normal mucosa, and non-enlarged inferior conchae. A biopsy was performed on the head of the right inferior concha under local anesthesia. Nasal packing with Merocel was required to stop mild bleeding over the next 24 h.

**Results**

**Case 1.** The biopsy revealed fragments of sinonasal mucosa, some with a polypoid shape showing marked interstitial edema and slight inflammation. CR staining showed amyloid deposition in areas of nasal mucosa not affected by edema and inflammation, and also at the base of polyps. Large amyloid deposits occurred mainly as interstitial masses, focally surrounding cavernous vascular structures. Diagnosis of FAP was confirmed; deposits were strongly positive for TTR IHC (Fig. 1); and AA and immunoglobulin light chains were negative.

![Fig. 1. Case 1: Massive dark-stained amyloid deposition in the lamina propria of the sinonasal mucosa, without relationship with surface epithelium (arrow) or mucus glands (stars) (TTR IHC 100×).](image1)

![Fig. 2. Case 2: Mucosa from inferior nasal concha. Extensive interstitial amyloid deposits, more extensive in deeper areas (arrows: surface epithelium) (TTR IHC 100×).](image2)
Case 2. The biopsy showed normal nasal mucosa. CR staining demonstrated extensive interstitial amyloid deposition, mostly dispersed, in the form of aggregates of variable size, and sometimes forming large clusters. Diagnosis of FAP was achieved as deposits were strongly positive for TTR with the IHC panel used in the Case 1 (Fig. 2).

Discussion

We report the first 2 patients with FAP diagnosed by finding ATTR in nasal mucosa. The biopsy was retrospective in the first case. We underline the usefulness of this retrospective analysis of biopsies in live and deceased patients relatives of probands with symptoms compatible with FAP, because in the cases with positive results a further biopsy is avoided and the familial incidence increased. In the second patient the biopsy was prospective on the inferior nasal concha which has easy access and harbors the appropriate characteristics for biopsies: low aggressivity, minimal morbidity, high efficiency and low cost.

In both patients the interstitial deposits of ATTR were extensive and readily identifiable with appropriate stains, suggesting that lamina propria stroma of this anatomical area is particularly prone to the deposition of systemic amyloid. Moreover, the high degree of deposits was present in the first stage of FAP: 1.5 years in the first patient and 6 months in the second. For these reasons, we suggest nasal mucosa as a suitable site for tissue biopsy in patients with suspected hereditary TTR amyloidosis.

Conflict of interest

The authors declare no conflict of interest.

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References