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Case Report

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Misunderstood case of tuberous sclerosis: can the bone evaluation be a helpful guide in the diagnostic challenge?

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1. Abstract

Tuberous sclerosis (TS) is a genetically determined disorder with tendency to hamartomas in various tissues. Due to its rare prevalence and clinical heterogeneity, the diagnosis is often delayed or even missed. This should be avoided considering promising therapeutic strategies and life-threatening complications. Bone lesions do not fall within major or minor criteria; however, they have typical features and tissue distribution that can be considered pathognomonic. This could be considered as a new potential imaging biomarker in asymptomatic or paucisymptomatic patients.

We describe a case report of a 60-year-old woman referred to our emergency department for worsening right flank pain in which the bone careful evaluation on CT scan allowed to pose the diagnostic suspicion of TS.

2. Introduction

Tuberous sclerosis (TS) is a rare autosomical dominant disease (incidence of 1:6000) [1]. 80% of cases are correlated with TSC1 or TSC2 genes mutation that encode for the mTOR pathway proteins hamartin or tuberin, respectively; genetic mutation is sporadic and spontaneous, without family history of TS [2]. The disease is characterized by multiple mesenchymal tumors [3]; the most commonly clinical manifestation are: skin lesions (hypopigmented macules and facial angiofibromas), cortical or subependymal brain tubers (frequently calcific), white matter abnormalities, retinal phakoma, multiple and bilateral renal angiomyolipomas, renal cysts, cardiac rhabdomyoma, thoracic lymphangioleiomyomatosis (LAM), and sclerotic bone lesions [4].

Clinical pattern of TS is highly variable depending on age [4]. In its typical form it occurs in childhood with seizures, intellectual disability and skin lesion (Vogt triad) [4]. Unfortunately, this is only seen in a minority of cases (~30%). In adults, the typical clinical manifestations are acute retroperitoneal bleeding and renal failure [5].

TS diagnosis is delayed or even missed because of atypical clinical signs and low prevalence. This should be avoided considering the possibility of promising therapeutic strategies (mTOR- inhibitors) and the high lifetime risk of life-threatening complications [6-10]. The International Tuberous Sclerosis Complex Consensus Group have most recently updated the diagnostic criteria [2] (Table 1). Current diagnostic guidelines are based on a typical combination of brain, kidney, skin, lung and heart clinical signs. When patients do not meet these criteria, it is sometimes defined as a TS “fruste forme”. A recent consensus conference emphasized the need for additional diagnostic biomarkers to improve the accuracy of TS

diagnosis [11]. Bone alterations, although very frequent (40-66%) and with typical characteristics [1,4], do not fall within major or minor criteria. A recent retrospective study proposed the evaluation of the sclerotic bone lesions (SBL) as a potential new additional imaging biomarker in the diagnosis of TS [1]. We describe the case of an oligosymptomatic adult patient in which the careful evaluation of the bone findings, accidentally discovered on CT examination, allowed us to diagnose TS.

Table 1: Updated diagnostic criteria for tuberous sclerosis complex 2012

Genetic Diagnostic Criteria	The identification of either a TSC1 or TSC2 pathogenic mutation in DNA from normal tissue is sufficient to make a definite diagnosis of tuberous sclerosis complex (TSC). Note that 10% to 25% of TSC patients have no mutation identified by conventional genetic testing, and a normal result does not exclude TSC, or have any effect on the use of clinical diagnostic criteria to diagnose TSC.
A. Clinical Diagnostic Criteria	*Major features* 1. Hypomelanotic macules (≥3, at least 5-mm diameter) 2. Angiofibromas (≥3) or fibrous cephalic plaque 3. Ungual fibromas (≥2) 4. Shagreen patch 5. Multiple retinal hamartomas 6. Cortical dysplasias* 7. Subependymal nodules 8. Subependymal giant cell astrocytoma 9. Cardiac rhabdomyoma 10. Lymphangioleiomyomatosis (LAM)† 11. Angiomyolipomas (≥2)† *Minor features* 1. "Confetti" skin lesions 2. Dental enamel pits (>3) 3. Intraoral fibromas (≥2) 4. Retinal achromic patch 5. Multiple renal cysts 6. Nonrenal hamartomas
Definite diagnosis: Two major features or one major feature with ≥2 minor features	
Possible diagnosis: Either one major feature or ≥2 minor features	

*Includes tubers and cerebral white matter radial migration lines.
† A Combination of the two major clinical features (LAM and angiomyolipomas) without other features does not meet criteria for a definite diagnosis.

3. Case Report

A 60-year-old female was referred to our emergency department for worsening right flank pain, without fever; inflammatory marker tests were negative. She did not report asthenia, nor weight loss but only some previous episodes of epilepsy. Computed Tomography (CT) scan with intravenous iodinated contrast agent showed multiple small, hypodense non-enhancing liver lesions less than 5 mm, not communicating with the biliary tree (Figure 1); CT also showed innumerable, small, subcortical, sclerotic bone lesions of pelvis and lumbar spine (of both vertebral body and posterior vertebral arches), with average densitometric values greater than 1000 Hounsfield Unit (HU), dimensions ranging from few to 8 mm, without cortical disruption nor periosteal reaction (Figure 2 a, b, c). On the basis of their detailed qualitative and quantitative evaluation, the radiological diagnostic hypothesis was of multiple accidental enostoses with a distribution pattern compatible with TS [1].

However, bone lesions do not fall within TS diagnostic criteria; then a multidisciplinary team evaluation suggested second level diagnostic investigations, to exclude an underlying neoplastic pathology. Mammography, breast ultrasound, gastroscopy, colonoscopy, and neoplastic markers blood test. A second total body CT and bone scan were performed. Second level investigations were unremarkable as well as neoplastic biomarkers. Total body CT examination confirmed multiple liver lesions (probably biliary hamartomas) and further small bone lesions localized also in the cervico-thoracic spine and in the cranial bones (Figure 3 a, b), with analogous characteristics of the lumbar and pelvic ones; no renal angiomyolipomas were found. It also documented some bilateral calcific subependymal brain nodules; these findings were confirmed to a subsequent MRI examination (Figure 4 a, b). No further peripheral bone lesions were detected (Figure 5). Bone scan did not reveal areas of radiopharmaceutical pathological accumulation (Figure 6).

Finally, after a long clinical and instrumental diagnostic process it was possible to define the diagnosis of TS on the basis of the presence of some of the major and minor criteria: hypomelanotic skin macules, subependymal nodule, and probable hepatic biliary hamartomas.

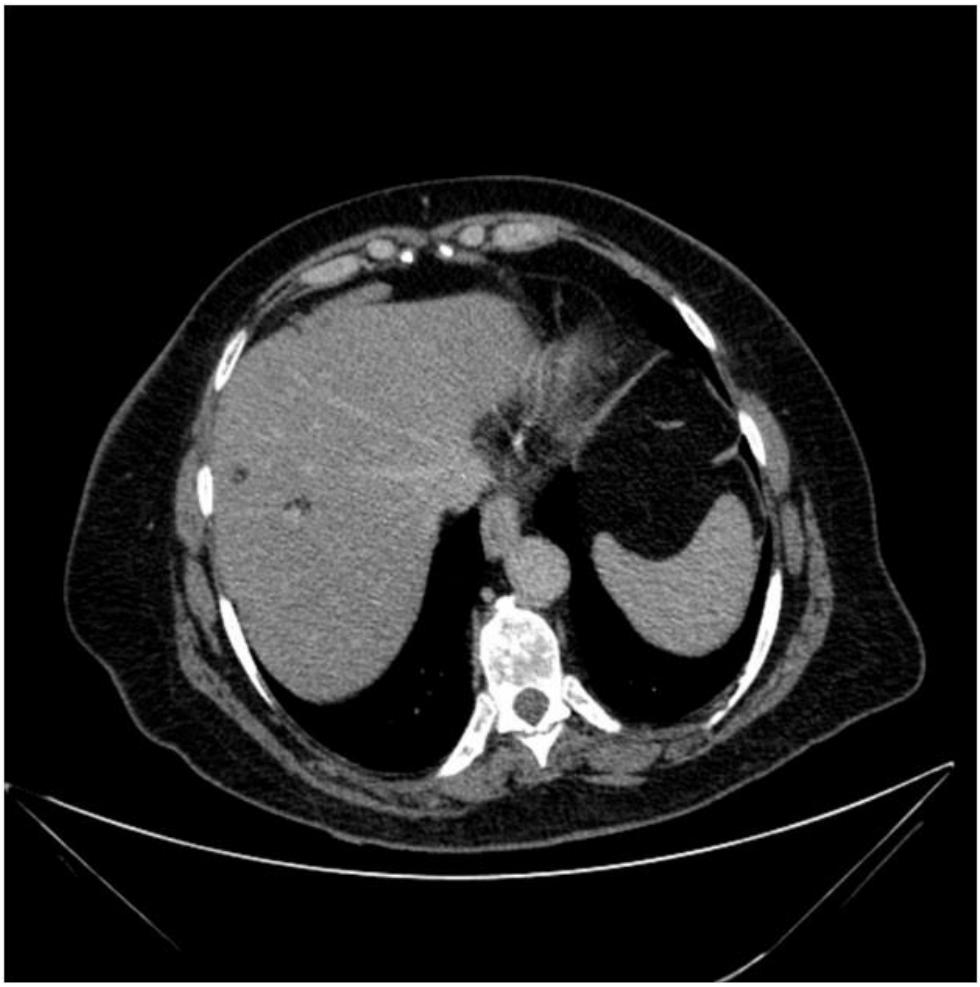

Figure 1: Computed Tomography (CT) scan in venous phase shows smultiple small hypodense non- enhancing liver lesions (less than 5mm) not communicating with the biliary tree; the most probable diagnostic hypothesis is hepatic biliary hamartomas.

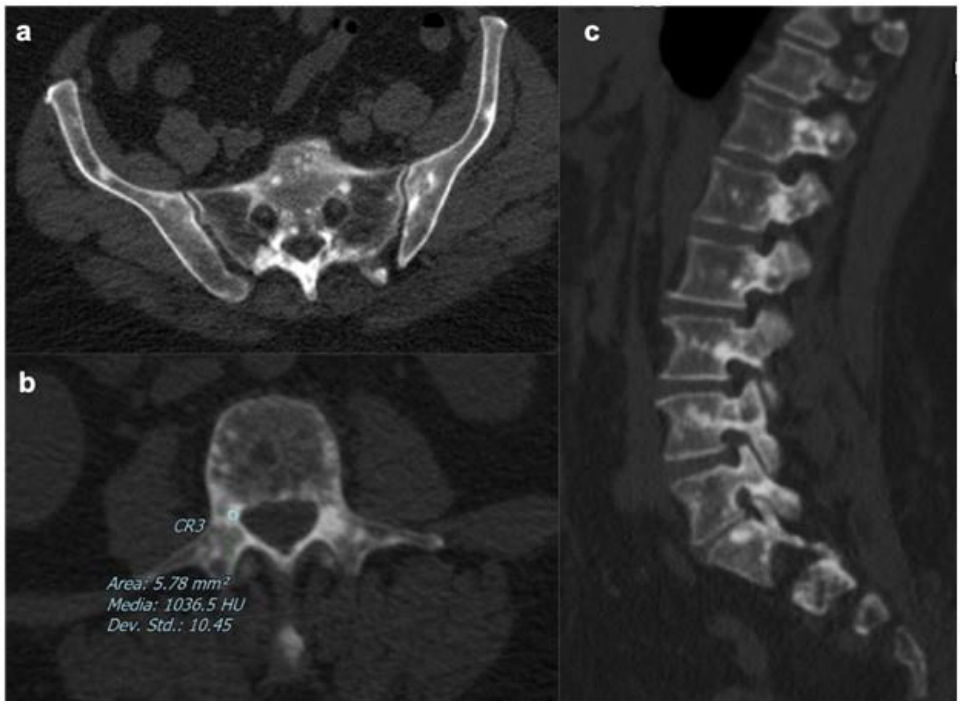

Figure 2: Axial (a, b) and sagittal (c) CT images show innumerable small subcortical sclerotic lesions of pelvis and lumbar spine (of both vertebral body and posterior vertebral arches), with average densitometric values greater than 1000 Hounsfield Unit (HU), dimensions ranging from few mm to 8 mm; no cortical disruption nor periosteal reaction. On the basis of CT semeiotics and distribution pattern, the first radiological diagnostic hypothesis was of TS sclerotic bone lesions.

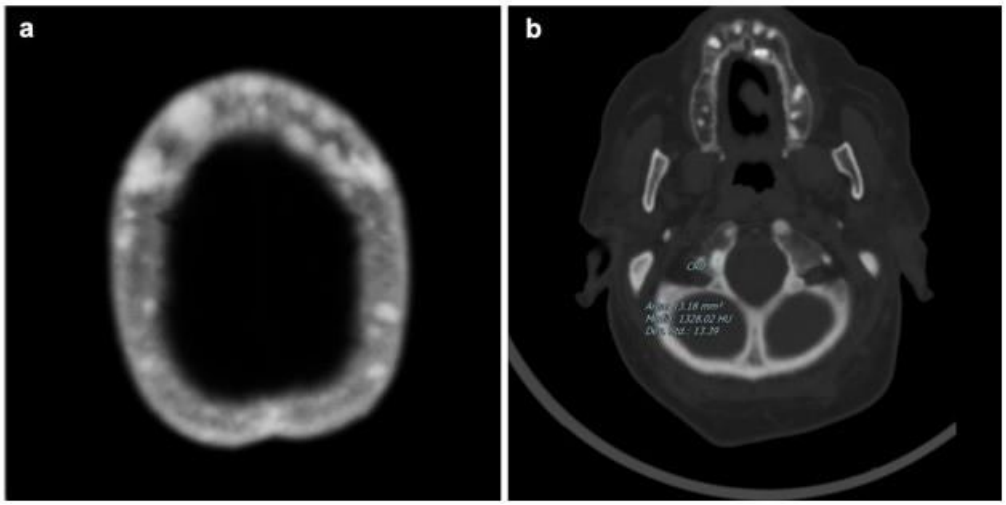

Figure 3: Axial CT (a, b) images show further small bone sclerotic lesions in the skull, with analogouscharacteristics to the lumbar and pelvic ones.

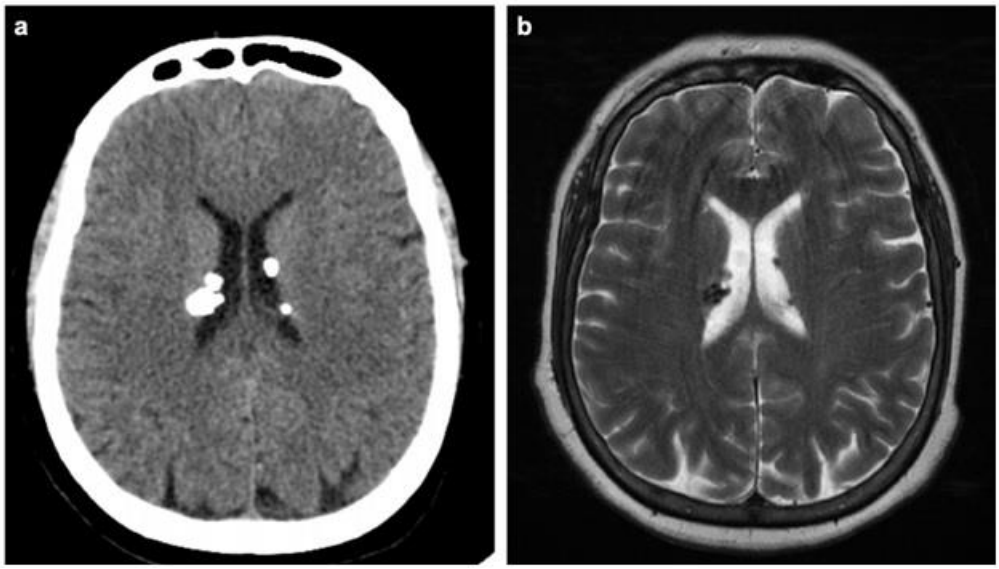

Figure 4: Axial CT (a) and T2-w MRI (b) images show bilateral calcific subependymal brain nodules.

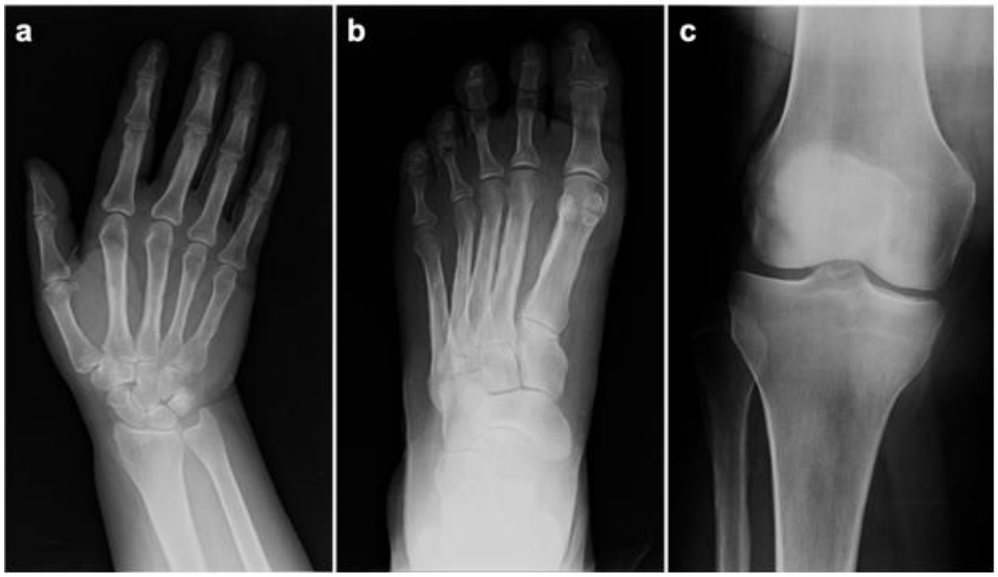

Figure 5: In addition, radiographic examination of the limbs excluded further peripheral bone lesions.

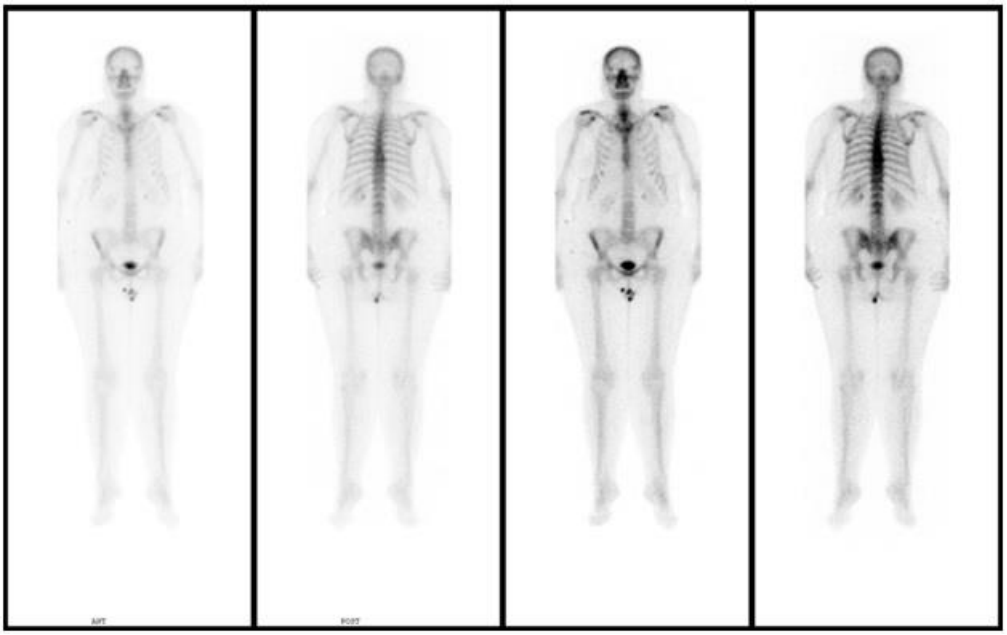

Figure 6: Bone scan does not reveal any area of radiopharmaceutical pathological accumulationcompatible with secondary lesions.

4. Discussion

TS diagnostic criteria have recently been updated [2] (Table 1) and a recent consensus conference emphasized the need for additional diagnostic biomarkers to improve the disease detection [11]. Generally, the incidental finding of multiple sclerotic bone lesions has always been a diagnostic challenge for the radiologist. Even in patients with TS, bone lesions could be misunderstood for bone metastases on imaging.

However, TS bone lesions have pathognomonic characteristics: they are enostoses with a specific distribution pattern.

Enostoses (also known as "bone island") are bone hamartomas [12]: cortical bone in the context of the spongiosa, most frequently seen in the spine, pelvis, and epiphyses or metaphyses of the long bones. Typically they are small and subcortical, oblong along the axis of the diaphysis or rounded in the metaphyses or short bones, with spiked margins that merge with the bony trabeculae; they are homogeneously dense sclerotic focus with high density: CT values greater than 885 HU represent a sensitive and specific cut-off in the differential diagnosis with sclerotic bone metastases [12]. When reexamined on serial imaging, as many as 31% of enostoses will change in size; the diameter of their growth, however, is expected to show a less than 25% increase in size over 6 months or 50% in 1 year. Biopsy should be considered for any lesion exceeding this growth rate [13]. Enostosis should have homogeneously low signal on all MRI pulse sequences, similar to cortical bone, without surrounding edema [13]. An MRI finding that should raise concern for a sclerotic bone metastasis is a rim of abnormal increased T2 signal in the surrounding marrow, a finding termed "halo sign". Although it is not present in all sclerotic metastases, when encountered, halo sign should prompt biopsy because there is a reported 99% specificity of this finding for metastasis [13]. On 99mTc–methylene diphosphonate bone scans, most enostoses will show radiotracer accumulation similar to that of background bone. However, enostoses may be warm or even hot on bone scans, especially for those greater than 2 cm [13,14]. Histopathologic examination of scintigraphically active bone islands showed increased osteoblastic activity, and the lesions were marked by a mixture of compact and trabecular bone. Therefore, a practical algorithm for examining bone islands should flow from their morphologic features as observed on radiographs and CT and MRI scans, rather than from their activity on scintigraphy [14]. Enostoses in TS patient are mainly localized in skull, spine (affecting both the body, the posterior arches and the spinous processes) and pelvis, unlike osteopoikilosis in which multiple enostoses affect the appendicular skeleton [15]; other bony structures (eg. sternum, ribs or femur) were affected, but to a lesser extent.

A recent retrospective study [1] analyzed size, frequency and location of sclerotic bone lesions (SBLs) in skull, thorax, and abdomen/pelvis in TS patients. The average size of SBLs was 4/5 ± 2 mm. Moreover, based on the number of SBLs, different diagnostic cutoffs could be calculated for each bone region. For example, in the skull and thorax bone, a frequency of ≥5 and ≥4 SBLs respectively yielded the optimal cutoff value for a reliable diagnosis of TS. The combination of SBL frequencies from two imaging regions resulted in a further improvement of sensitivities and specificities: for example, if SBL frequency data from skull and thorax were combined, SBL cutoff values of ≥5 and ≥4 resulted in a sensitivity of 0.99 and a specificity of 1. Therefore, sclerotic bone lesions can be considered as a potential imaging biomarker in the diagnostic challenge: a diagnosis of TS can be suspected based on the features, frequency, size and location pattern of the bone lesions. This could be especially important first for oligosymptomatic patients and/or younger patients, who do not fully meet the diagnostic TS guideline criteria, and second in all patients with undiagnosed TS,

in which a CT scan is performed due to other clinical indications. In these patients, the recognition of SBLs as a typical imaging sign of TS could represent the crucial connection towards a timely diagnosis and, if indicated, a specific therapy.

Our case report confirm what was demonstrated in the study of Brakemeier et al [1]; we wanted to underline how the careful qualitative and quantitative analysis of bone lesions has allowed the radiologist to put the diagnostic hypothesis of TS ab initio, even in the absence of other typical alterations of the disease; however, since bone alterations are not within the diagnostic criteria of the disease, this was not sufficient to make a definitive diagnosis and to avoid further costly and time-consuming diagnostic investigations.

5. Conclusion

Can the bone evaluation be a helpful guide in the diagnostic challenge of TS? The answer to this provocative question is certainly yes. Indeed, bone lesions have pathognomonic features and therefore could serve as a new potential imaging biomarker in diagnostic guidelines, above all in asymptomatic or paucisymptomatic patients. This is of great clinical relevance in order to avoid further useless and expensive diagnostic investigations, patient's apprehension, and late or even missed diagnosis, considering the possibility of promising therapeutic strategies and the high lifetime risk of life-threatening complications.

6. Funding

This study has no financial support.

7. Conflict of Interest

The authors declare that they have no conflict of interest.

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