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HOW TO DEAL WITH PHEOCHROMOCYTOMA IN 2022

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ABSTRACT

Pheochromocytomas and paragangliomas are rare neuroendocrine tumors associated with fairly high morbidity and mortality, especially in complicated forms. If hypertension is the often-revealing clinical manifestation, clinical presentations remain polymorphic and the diagnosis is essentially based on the biological assay of catecholamine derivatives associated with morphological and functional radiological examinations. Computed tomography and magnetic resonance are very sensitive to localize these tumors, and functional tests are useful, especially in metastatic and multifocal disease case suspicion. More than 30% of patients have a genetic predisposition with many genes that are involved especially in its familial forms.

KEYWORDS: Pheochromocytoma; Paraganglioma; Catecholamines; Genetic predisposition.

I- INTRODUCTION AND BACKGROUND

A pheochromocytoma (PHEO) is a rare tumor arising from the chromaffin cells of the adrenal medulla. This tumor produces excessive catecholamines: adrenaline, noradrenaline, and dopamine.[1] PHEO or intra-adrenal paragangliomas according to the 2004 WHO's definition, represent approximately 85% of cases.[2,3] The remaining 15% are extra-adrenal tumors (EAP). The latter occupy several anatomical locations in the body and are classified as sympathetic or parasympathetic based on their location and neural association.[4] It is a rare

cause of arterial hypertension which nevertheless remains important to diagnose because of the lethal risk that can occur during complications, especially acute hemodynamics.[5]

Diagnosis is based on the measurement of methoxyl derivatives of plasma and urinary catecholamines and on anatomical and functional imaging.[3] The annual incidence of PHEO is estimated at 0.4 to 9.5 per 1 million individuals per year,[4] and their prevalence in the population at 0.05 to 0.12%.[2] They concern 0.1 to 0.2% of hypertensive patients[3] and between 1.8 to 18% of incidentalomas discovered on computerized tomography (CT) for any other abdominal disease[6] The maximum age of onset is in the third to fifth decades of life.[7] but 10 to 20% are discovered during childhood. There is a slight predilection in females (55.2%) than males (44.8%).[2]

Previously, PHEOs/Paraganglioma (PGLs) were said to follow the "rule of 10s": 10% occurring in extra-adrenal tissue, 10% bilateral, and 10% malignant. Later, the parameter that 10% of these tumors were familial was added to this rule.[7] Although this rule persists in many medical textbooks and courses, recent studies have shown that the "rule of 10" no longer applies.[4] The sporadic forms are the most frequent, but in the hereditary family forms, the pheochromocytoma appears at an earlier age, it is bilateral from the outset or during evolution, it is frequent in multiple endocrine neoplasia type 2 (MEN 2) (about 50%), in Von Hippel Lindau disease (VHL) type 2 (10 to 30%) and in neurofibromatosis (1 to 4%).[6]

This work aimed to update the diagnosis of these tumors (Clinical, biological, and radiological) and explore their genetic characteristics.

II- Review

1- Clinical diagnostic

About 10% of pheochromocytomas are asymptomatic.[8] Hypersecretion of catecholamines (Epinephrine, Norepinephrine, Dopamine) is the cause of arterial hypertension which can be permanent systolic -diastolic and severe or exclusively paroxysmal in a third of cases).[3,9] Paroxysmal seizures are sometimes triggered by trauma, surgery, physical exertion, or certain medications.[9,10] The typical but not always constant presentation appears with the classic triad which associates headaches (peripheral vasoconstriction: alpha-adrenergic), palpitations (stimulation of beta-adrenergic receptors), profuse sweating (activation of alpha-adrenergic receptors in the sweat glands).[3] Less common signs and symptoms are fatigue, nausea,

weight loss, constipation, flushing, anxiety, fever, and high blood sugar.[3,7] Depending on the degree of catecholamine excess, patients may experience myocardial infarction, arrhythmia, or stroke and sudden death remains possible.[3,7]

Functional pheochromocytomas can also cause endocrine paraneoplastic syndromes (PNS) through the secretion of bioactive substances from tumor cells. The most frequently encountered PNS is Cushing's syndrome caused by adrenocorticotropic hormone or corticotropin-releasing hormone secretion.[4] The diagnosis of pheochromocytoma can also be made without any symptoms[3] in the assessment of an adrenal incidentaloma, in the context of genetic investigations for the detection of PHEO or PGL in first-degree relatives of affected subjects, or as part of the assessment of syndromes which may include PHEO (MEN, neurofibromatosis, VHL).

2- Biology diagnostic

The biological assessment plays an important role in the diagnosis of PHEO, by demonstrating an excessive increase in the synthesis of catecholamines. The dosage will be of interest to patients who respond to specific indications, in particular.[5] patients with signs suggestive of excess catecholamines; unexplained blood pressure instability; adrenal incidentalomas; young patients with hypertension; and genetic susceptibility.

Currently, biological tests are based on the determination of plasma fractionated metanephrines or 24-hour urinary fractionated metanephrines.[2] Indeed, these are the only two types of assays with a sensitivity greater than 95%. Consequently, the risk of false negatives is very low (about 1%).[5] Blood sampling should be performed in the supine position after approximately 15-20 min of catheter insertion[2] and should be collected after overnight fasting.[1] The elevation of plasma metanephrines more than 4 times above the upper reference limit is associated with a tumor probability close to 100%.[2] In patients with plasma metanephrine values above the upper reference limit and below 4 times above this limit, the combined clonidine suppression test may be useful.[2] For the determination of methoxylated derivatives of urinary catecholamines. Urine sampling is done on 24-hour urine or collected for a short period after a hypertensive attack and must be stored in an acid medium.[3]

Drug interference is the cause of false positives for plasma (tricyclic antidepressants, acetaminophen, paracetamol, etc.) and urinary (methyldopa, clonidine, beta-blockers,

tricyclic antidepressants, etc.) assays. Stopping these treatments, if possible, should precede the assessments by 2 to 3 weeks.[3] When possible, biochemical testing should always precede imaging, as this is the most cost-effective approach to diagnosing PHEO/PGL and if biochemical testing is negative, the patient is not subjected to further unnecessary radiation. However, in clinical practice, many patients with PHEO/PGL present with a mass accidentally discovered on imaging, and then they will benefit from a biological evaluation.[7]

3- Imaging diagnostic

Represented by CT, magnetic resonance imaging (MRI), and functional imaging, it is the best tool for tumor localization.[4]

a- CT scan

Abdominopelvic CT is the first-line examination. About 95% of pheochromocytomas are located in the abdomen (including 5 to 10% outside the adrenal glands). Perform without and with an injection of venous contrast product.[3] CT sensitivity is very good for adrenal pheochromocytomas. It can detect pheochromocytomas 1-2 cm in diameter.[3] The tumor mass can be homogeneous or heterogeneous, necrotic with calcifications, or sometimes solid or cystic with massive contrast enhancement due to the richness of their capillary network (Figures *1*,2,3,4,5,6,7). PHEOs can be reliably excluded in the case of adrenal injury with an unimproved attenuation value of 10 HU or less.[11]

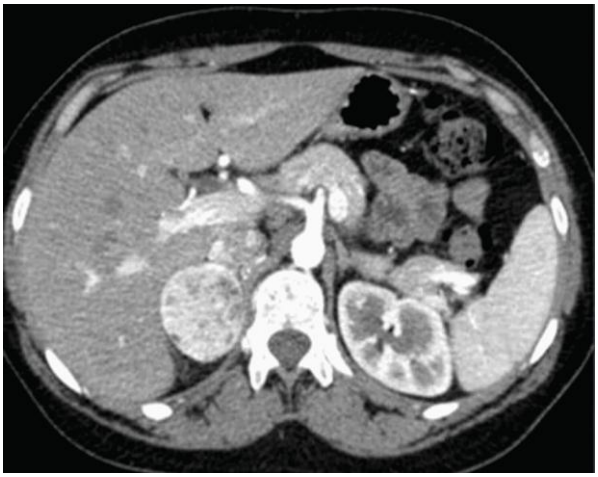

Figure 1: Abdominal CT scan (axial section) with contrast agent injection in arterial phase passing through the adrenals: rounded and well-limited right adrenal lesion with intense enhancement after injection of contrast agent.

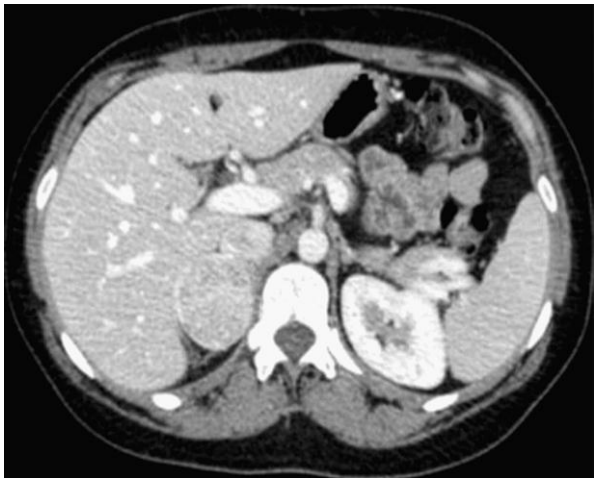

Figure 2: Abdominal CT scan axial section with contrast agent injection in portal phase.

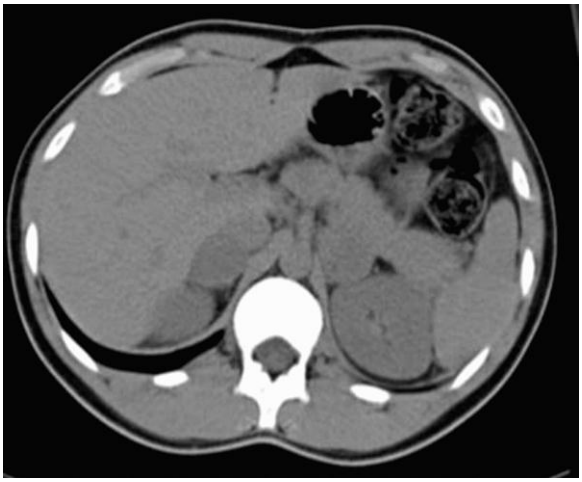

Figure 3: Abdominal CT scan, axial section without PDC injection.

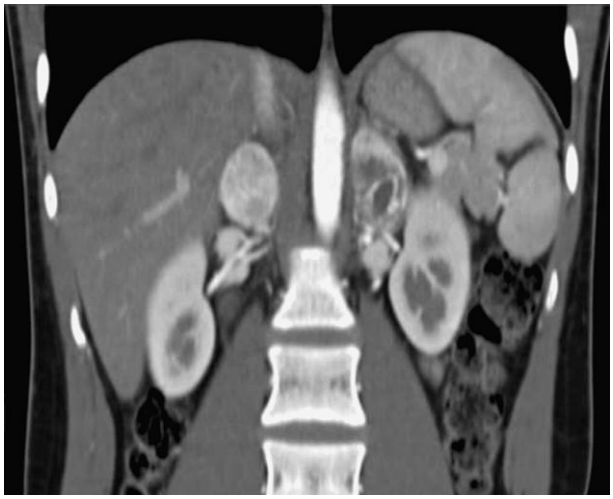

Figure 4: Abdominal CT scan coronal section with contrast agent injection in arterial phase, passing through the adrenal glands: bilateral adrenal lesion isodense with intense enhancement after injection of contrast agent.

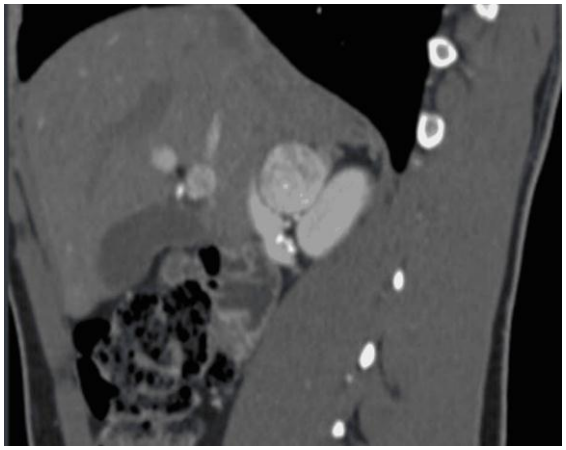

Figure 5: Abdominal CT scan, sagittal section with contrast agent injection in arterial phase, passing through the right adrenal gland.

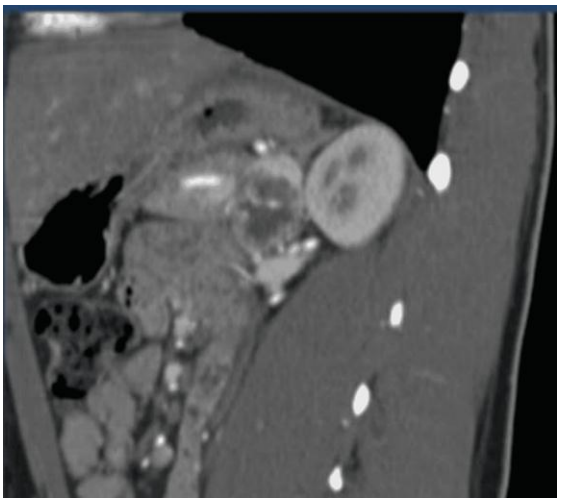

Figure 6: Controlateral adrenal gland in sagittal section showing the same radiological semiology as the previous figure.

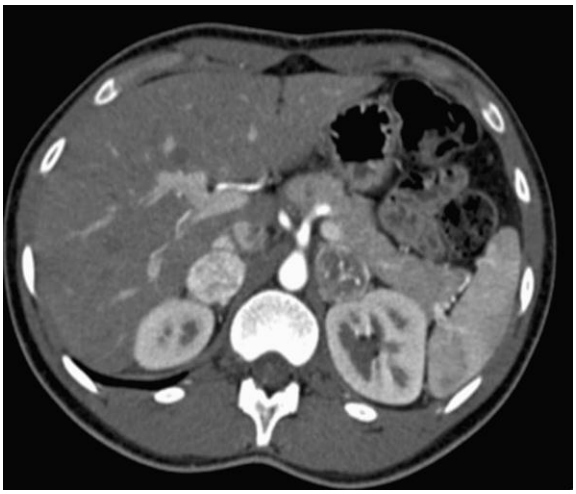

Figure 7: bilateral adrenal lesion in axial section with contrast agent injection in arterial phase.

***b*- Magnetic resonance imaging**

MRI is the first choice in children, pregnant women, and breastfeeding mothers, it is more efficient for the detection of paragangliomas (head, neck, intracardiac, pericardial, or perivascular). It can be used when the CT scan is negative.[3] The attenuation values of pheochromocytomas are often similar to those of muscle tissue and are significantly higher than those of adrenal adenomas.[1] Pheochromocytomas are usually in intense hypersignal on T2-weighted images (light bulb sign),[8] comparable to CSF signal intensity.[2]

***c*- Functional imaging**

Functional examinations in addition to CT/MRI anatomical explorations allow better localization and characterization of pheochromocytomas. Various substances have been used for functional imaging of pheochromocytoma,[2] scintigraphy with meta-iodobenzylguanidine (MIBG = norepinephrine analog) labeled with I123 or I131 of the whole body, 111In-pentetreotide (Octreoscan) and several PET ligands, including (18)F-fluorodopamine [(18)F-FDA], (18)F-fluorodihydroxyphenylalanine [(18)F-FDOPA], and (18)F-fluoro-2-deoxy-D-glucose [(18)F-FDG].[3]

MIBG scintigraphy: Imaging using MIBG is the most common and available functional imaging technique, used in the evaluation of PHEO, very useful for the search for paragangliomas and multifocal forms,[3] MIBG scintigraphy has a sensitivity varying between 80% (I131 MIBG) to 90% (I123 MIBG), and high specificity (90%).[5] MIBG is a norepinephrine analog that localizes first to presynaptic adrenergic nerves and sympathomedullary tissue through an active amine transport system and then to cytoplasmic storage vesicles. The absorption of the radiotracer is proportional to the number of neurosecretory granules in the tumor.[2] It is indicated in familial forms, malignant forms, and cases of negative anatomical imaging.[3] MIBG scintigraphy should no longer be performed routinely preoperatively in a patient with a certain biological diagnosis and whose imaging (CT-MRI) shows a certain and unique unilateral adrenal lesion.[5]

Pentetreotide scintigraphy (Octreoscan®): Indium-111 pentetreotide is an analogue of somatostatin. PHEO can express somatostatin receptors, which allows the use of pentetroteotide in the diagnostic process.[2]

Positron emission tomography (PET) scanner: Currently, PET with a specific tracer, PET (18)F-FDOPA and PET F-FDA is being studied with very promising results in cases of

difficult diagnosis.[3] Pet -scanner (18)F-FDOPA remains more efficient than MIBG scintigraphy in the detection of distant metastases.[5] and is the preferred diagnostic modality in these cases, even compared to total body MRI,[12] but its low availability limits its widespread use.

There is some debate about the role of functional imaging in the preoperative evaluation of Pheo /PGL,[7] most researchers would agree that when there is a high biochemical probability of PHEO/PGL and a low probability of metastasis (small tumor, adrenal location, adrenergic phenotype, non-SDHB) that CT or MRI is adequate. If, however, metastatic disease is suspected or when CT or MRI fails to localize the lesion, functional imaging may be warranted.[7]

4- Diagnosis of malignancy

The majority of pheochromocytomas are benign; however, some may show the potential for malignancy in 10-15%.[8]

To date, the only universally accepted criterion for establishing the malignancy of a pheochromocytoma remains the presence of invaded lymphadenopathy or distant metastases in a site that does not contain chromaffin tissue.[5] The question of the malignancy of a pheochromocytoma is important in practice because the secondary appearance of metastases (± local recurrence) has been observed in up to 7% of patients within periods of up to 15 years after a resection surgery for an “apparently benign” tumor.[5] Malignant potential is higher in PHEOs >5 cm in size, extra-adrenal tumors, and familial cases with mutations (SDHB),[4] but neither tumor size, mitotic rate, vascular invasion, or capsular do not constitute a sufficient distinguishing characteristic to distinguish benign tumors from malignant tumors.[2] Several studies have evaluated different combinations of histological and/or biological criteria without always reaching the same conclusions.[13-15] In 2002, Thompson[16] had proposed the combined Pheochromocytoma of Adrenal Gland Scaled Score (PASS) of 12 histological parameters, more frequently observed in malignant tumors than in benign tumors (rated either 0 or 1, or 0 or 2) with a total of 20 points (Table *1*).[16]

Table 1: PASS score [16]: score less than` 4 in favor of benignity, score greater than or equal to` 4 in favor of aggressive potential.

Criteria	Rating if present
Large islands/diffuse architecture (> 10% of tumor volume)	2
Necrosis localized in the center of the islets or confluent	2
High cellularity	2
Cell monotony	2
Fusiform aspect (even if focal)	2
Mitoses > 3/10 hpf	2
Atypical mitoses	2
Adipose tissue infiltration	2
Vascular invasion	1
Capsular infiltration	1
Marked nuclear pleomorphism	1
Nuclear hyperchromatism	1
Total	20

Recently validated, the Grading system for the adrenal pheochromocytoma and paraganglioma (GAPP) is used for both pheochromocytomas and paragangliomas and integrates both clinical and histological parameters (table *2*).[17] The GAPP provides a progressive assessment of metastatic risk and patient survival, the histological classification is based on a scoring system composed of 6 parameters considered as risk factors for metastasis, a maximum of 10 points is possible.[4] A neoplasm with an overall score ranging from zero to 2 points is considered well differentiated, a tumor with an intermediate score ranging from 3 to 6 points is defined as moderately differentiated, and a score greater than or equal to 7 is considered poorly differentiated (Table *3*).[4]

Table 2: Grading system for the adrenal Pheochromocytoma and Paraganglioma (GAPP).[17]

Settings	Points awarded
Histological Pattern	
• **Classic zellballen**	0
• **Wide and irregular cell nest**	1
• **Pseudorosette**	1
Cellularity	
• **Low (<150 cells /U)**	0
• **Moderate (150–250 cells /U)**	1
• **High (>250 cells /U)**	2
Comedy necrosis	
• **Absence**	0
• **Presence**	2
Vascular or Capsular Invasion	

• **Absence** • **Presence**	0 1
Ki67 Proliferative Index (%) • **<1** • **1–3** • **>3**	 0 1 2
Catecholamine Type • **Epinephrine** • **Norepinephrine** • **Nonfunctioning**	 0 1 0
Total points	10

Table 3: (GAPP) score and histological grade.[4]

GAPP score	Histological grade
0-2	well differentiated
3-6	moderately differentiated
7-10	poorly differentiated

The prognosis of malignant pheochromocytomas remains poor with only 10% survival at 5 years,[8] and the most common metastatic sites are the bones, lungs, liver, and lymph nodes.[18]

5- Anatomo-pathological confirmation

The histological diagnosis of pheochromocytoma does not generally pose a problem. In macroscopy, they are well-circumscribed but generally not encapsulated. In cross-section, they have a firm rubbery consistency and vary from pale pink to dark reddish-brown, probably secondary to their well-established vascular network.[4] They may present with degenerative cystic changes with associated fibrosis and/or haemorrhage.[4] Cytologically, the main chromafin cells are fairly monomorphic polygonal cells with basophilic granular cytoplasm and round vesicular nuclei, pleomorphism with nuclear pseudo inclusions or prominent nucleoli. Marbled and oncocytic cells may be seen but usually comprise a small percentage of the tumor. Intracytoplasmic hyaline globules are often present. Necroses and mitoses are rare and may raise suspicion of more histologically aggressive behaviour.[4]

The immunohistochemical study is not generally necessary for the positive diagnosis of pheochromocytoma, it shows positivity for chromogranin A, synaptophysin, and CD56 (group of differentiation 56) but does not express epithelial markers, with a characteristic network of suprastentacular cells visible with the S100 protein surrounding the tumor cells.[6] Other markers, such as catecholamines, neuron-specific enolase, and neurofilm, can be

expressed. If the cells do not stain for chromogranin A, the diagnosis of PPGL should be reconsidered.[4]

6- Genetic exploration

Over 30% of pheochromocytomas and paragangliomas are genetically predisposed.[9] Recent studies suggest that up to 41% of patients have a germline mutation in one of the known common susceptibility genes (including NF1, VHL, RET, SDHB, SDHD, SDHC).[19,20] The most frequently mutated gene was SDHB, which presents the highest risk of malignancy.[19]
A systematic genetic investigation is recommended more particularly in the familial forms, the forms of early-onset, and in the presence of suggestive clinical signs (café-au-lait spots, medullary cancer of the thyroid).[3] patients with multifocal tumors, extra-adrenal tumors, and bilateral tumors are more likely to have a genetic predisposition.[20-21]

The nature of the genetic tests is determined according to the family study, the clinical examination of the patient, and the characteristics of the pheochromocytoma (table *4*).[3] The genetic investigation must be carried out after having explained its interest to the patient and after obtaining his informed consent, in compliance with the regulations.[9]

Several autosomal dominant hereditary diseases include in their picture a pheochromocytoma or a paraganglioma. These family forms are earlier than the sporadic forms; they occur before the age of 50 and include all pheochromocytomas in children. Among these familial forms are:[7] the multiple endocrine neoplasia type 2 (MEN 2A and MEN 2B); Von Hippel Lindau disease (VHL); neurofibromatosis type 1 (NF1) or Recklinghausen disease; and Pheochromocytomas and paragangliomas linked to SDH gene mutations.

Table 4: Orientation of genetic tests based on clinical information.

Clinical information	Genetic tests
Cafe´-au-lait stains	NF1
Medullary thyroid carcinoma _	RET
Hyperparathyroidism Hemangioblastoma	RET
tumor renal	VHL
Paraganglioma head and neck	SDHB, SDHC
Malignant pheochromocytomas	SDHB
Pheochromocytomas bilateral	RET, VHL

In a patient with pheochromocytoma or paraganglioma, the demonstration of a genetic predisposition allows[9] to adapt the therapeutic management and the methods of monitoring

the patient himself and to propose a family study in order to identify relatives carrying the same mutation who will thus be able to benefit from screening protocols and early therapeutic care. The genetic test must be prescribed by a medical specialist, within the framework of a specialized oncogenetic consultation. Psychological support is essential throughout the family investigation.[9]

III- CONCLUSIONS

Pheochromocytomas and paragangliomas are rare neuroendocrine tumors associated with fairly high morbidity and mortality, especially in complicated forms. Their diagnosis implies a good knowledge of their clinical presentation and a better interpretation of biochemical tests whose main role is to show the excess secretion of catecholamines and their metabolites. Computed tomography and magnetic resonance are very sensitive for locating these tumors and are sometimes associated with functional examinations, especially in the event of suspicion of metastatic and multifocal disease. More than 30% of patients have a genetic predisposition with many genes that are involved especially in its familial forms.

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