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Lymphadenopathy with high PET-CT uptake: a case of mixed connective tissue disease mimicking lymphoma

Linfadenopatia com alta captação em PET-CT: um caso de doença mista do tecido conjuntivo mimetizando linfoma

Linfadenopatía con alta captación PET-TC: un caso de enfermedad mixta del tejido conectivo que simula un linfoma

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ABSTRACT

Objective: To report a case of a Mixed Connective Tissue Disease (MCTD) that mimicked lymphoma during the diagnostic investigation. **Case details:** A 44-year-old woman was referred to a hospital with suspected lymphoma. She presented with a one-month history of lower limb weakness, accompanied by left lower limb paresthesia, asthenia, Raynaud's phenomenon, and a six-kilogram weight loss. Physical examination revealed an emaciated appearance with microstomia, reduced facial expression marks, sclerodactyly, skin thickening in the upper limbs, muscle weakness in all limbs, and lymphadenopathy in the left cervical and inguinal regions. Pulmonary auscultation revealed crackles at the lung bases. A PET-CT scan revealed increased uptake in the lymph nodes. During hospitalization, the patient tested positive for Anti-RNP antibodies, and the immunohistochemical analysis of a lymph node biopsy showed a reactive pattern. Based on the clinical and laboratory findings, a diagnosis of MCTD was made, and appropriate treatment was initiated. After six months of treatment, a new PET-CT scan showed the disappearance of the affected lymph nodes. **Final considerations:** MCTD is a rare, complex condition that can mimic other diseases, such as lymphoma, making early and accurate diagnosis essential.

Keywords: Mixed connective tissue disease, Lymphoma, Positron emission tomography computed tomography.

RESUMO

Objetivo: Relatar um caso de Doença Mista do Tecido Conjuntivo (DMTC) que mimetizou linfoma durante a investigação diagnóstica. **Detalhamento do caso:** Uma mulher de 44 anos foi encaminhada para um hospital com suspeita de linfoma. Ela apresentava uma história de um mês de fraqueza nos membros inferiores, acompanhada de parestesia no membro inferior esquerdo, astenia, fenômeno de Raynaud e perda de seis quilos. O exame físico revelou uma aparência emagrecida com microstomia, redução das marcas de expressão facial, esclerodactilia, espessamento da pele nos membros superiores, fraqueza muscular em todos os membros e linfadenopatia nas regiões cervical esquerda e inguinal. A ausculta pulmonar revelou

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estertores nas bases pulmonares. A PET-CT mostrou captação aumentada nos linfonodos. Durante a internação, a paciente apresentou positividade para anticorpos Anti-RNP e a análise imunohistoquímica da biópsia do linfonodo mostrou um padrão reacional. Com base nos achados clínicos e laboratoriais, foi feito o diagnóstico de DMTCe o tratamento adequado foi iniciado. Após seis meses de tratamento, uma nova PET-CT mostrou o desaparecimento dos linfonodos alterados. **Considerações finais:** A DMTC é uma condição rara e complexa que pode mimetizar outras doenças, como linfoma, tornando essencial o diagnóstico precoce e correto.

Palavras-chave: Doença mista do tecido conjuntivo, Linfoma, Tomografia por emissão de pósitrons combinada à tomografia computadorizada.

RESUMEN

Objetivo: Informar un caso de Enfermedad Mixta del Tejido Conectivo (EMTC) que imitaba un linfoma durante la investigación diagnóstica. **Detalles del caso:** Una mujer de 44 años fue derivada a un hospital con sospecha de linfoma. Presentaba un mes de debilidad en las extremidades inferiores, junto con parestesia en la extremidad inferior izquierda, astenia, fenómeno de Raynaud y pérdida de seis kilogramos. El examen físico mostró una apariencia delgada conmicrostomía, reducción de marcas faciales, esclerodactilia, engrosamiento de la piel en los brazos, debilidad muscular en las extremidades y linfadenopatía en las regiones cervical izquierda e inguinal. La auscultación pulmonar reveló crepitaciones en las bases pulmonares. Una PET-CT mostró mayor captación en los ganglios linfáticos. Durante la hospitalización, la paciente fue positiva para anticuerpos Anti-RNP, y el análisis inmunohistoquímico de la biopsia del ganglio linfático mostró un patrón reactivo. Con base en los hallazgos clínicos y de laboratorio, se diagnosticó EMTC y se inició el tratamiento. Tras seis meses de tratamiento, una nueva PET-CT mostró la desaparición de los ganglios afectados. **Consideraciones finales:** La EMTC es una enfermedad rara y compleja que puede imitar otras condiciones, como el linfoma, lo que hace crucial un diagnóstico temprano y preciso.

Palabras claves: Enfermedad mixta del tejido conjuntivo, Linfoma, Tomografía computadorizada por tomografía de emisíon de positrones.

INTRODUCTION

Mixed Connective Tissue Disease (MCTD) is a rare autoimmune disease characterized by a set of features from at least three other rheumatological diseases, Systemic Lupus Erythematosus (SLE), Systemic Sclerosis (SS) and Polymyositis or Dermatomyositis, associated with the presence of the anti-ribonucleoprotein U1 antibody (Anti-RNP), which is a specific marker for this disease that still has no well-defined etiology. (KATEWA R, et al., 2014; WANZENRIED A, et al., 2022; FRANCO AS and MIOSSI R, 2022).

MCTD was first described in 1972 by rheumatologist Gordon Sharp when he studied a group of people who had characteristics typical of other autoimmune diseases that were already well established at the time (SHARP GC, et al., 1972; FRANCO AS and MIOSSI R, 2022; SATO F, et al., 2023). With regard to epidemiological data, the incidence of MCTD is still not well established. A Norwegian study revealed a prevalence of 3.8 per 100,000 inhabitants among adults, with an incidence of 2.1 cases per million inhabitants per year, with most cases occurring in women around the age of 32 (GUNNARSSON R, et al., 2011).

There are various diagnostic criteria for MCTD. The criteria proposed by Sharp evaluated clinical and laboratory factors, divided into major and minor. The major criteria are based on typical features of systemic sclerosis, such as signs of pulmonary hypertension, Raynaud's phenomenon and esophagealhypomotility. The minor criteria, on the other hand, had a greater predominance of SLE characteristics such as alopecia, leukopenia, anemia, thrombocytopenia and pericarditis. If the patient presents four major criteria with the presence of anti-U1-RNP greater than 4,000 (hemagglutination) with negative anti-Sm, it defines MCTD (SHARP GC, et al., 1972).

The Alarcón-Segovia criteria are the most widely used in medical practice and include the presence of an anti-RNP titer greater than 1:1600 by the hemagglutination method and three of the following criteria: diffuse

edema of the fingers or hands, acrosclerosis, Raynaud's phenomenon, myositis and synovitis (ALÁRCON-SEGOVIA D and CARDIEL MH, 1989). Kasukawa's criteria include the following three conditions: common symptoms of the disease (Raynauld's and edema of the hands or fingers), serological marker (anti-RNP greater than 1:1000 by hemagglutination method) and presence of one or more findings from two or more disease categories (this item includes SLE, ES and polymyositis) (KASUKAWA R, 1987).

In 1991, Kahn and Appelboom described other criteria that are also accepted today for the diagnosis of CTCD. They are similar to the Alarcón-Segovia criteria and are based on mandatory serological criteria (Anti-U1-RNP present with a titer greater than 2,000) and clinical criteria (KAHN MF and APPELBOOM T, 1991). The Takata criteria, on the other hand, are the most recently established criteria and also include common clinical criteria (the same as the Kasukawa criteria), serological criteria (presence of anti-RNP at any titer in the ELISA or double immunodiffusion method) and the presence of at least one characteristic of two disease categories (also refers to SLE, SS and polymyositis) (TANAKA Y, et al., 2021).

The diagnosis of MCTD can also be established by the Takata criteria without the presence of the characteristics of other rheumatological diseases. It is enough to present a typical involvement of the disease (including only pulmonary hypertension, aseptic meningitis or trigeminal neuropathy) associated with the common clinical features and serological criteria (TANAKA Y, et al., 2021).

MCTD should be kept as a differential diagnosis when overlapping signs of autoimmune diseases are present, such as swelling in the fingers, arthralgia, myalgia, dysphagia and Raynaud's phenomenon. However, there is no data in the world literature showing Mixed Connective Tissue Disease to be a differential diagnosis of Lymphoma, nor showing such high uptake in PET-CT scans. Therefore, the aim of this study is to report the case of a 44-year-old patient diagnosed with MCTD whose initial diagnostic hypothesis was lymphoma due to the high uptake detected on PET-CT.

DETAILS OF THE CASE

This case report was approved by the Research Ethics Committee of the Centro Universitário Católico Salesiano Auxilium, UniSALESIANO-Araçatuba (CAAE 80159824.1.0000.5379 and Report Number 6.867.777). The Informed Consent Form was signed by the patient. A 44-year-old female patient was referred to a tertiary hospital from the municipal emergency department reporting weakness in her lower limbs for a month. In addition to weakness, the patient reported paresthesia in her left lower limb and progressive asthenia.

On colder days, she reported a change in the color of the fingers on both hands. She experienced unintentional weight loss of 6 kilograms during this period. No dyspnea, fever or joint pain was reported. No comorbidities. She mentioned a previous abortion 7 years ago. Regarding continuous medication, she reported using oral contraceptives regularly and nifedipine irregularly. On physical examination, the patient was emaciated with the presence of microstomia and a reduction in facial expression marks. Auscultation of the lungs showed a slight crackling rales at the bases, predominantly at the right lung base.

Cardiac auscultation showed no alterations. The abdomen was painless on superficial and deep palpation, with hepatomegaly extending 5 cm from the costal margin. Sclerodactyly and thickening of the skin were evident on both extremities of the upper limbs. There was muscle weakness in all four limbs. There was lymph node enlargement in the left cervical and inguinal chains.

The patient presented with laboratory tests carried out in a private laboratory with the following results: Antinuclear Factor (ANF) reactive at 1/320 with a dense fine dotted cytoplasmic pattern; Anti-Centromere antibody not reactive; Anti-Topoisomerase-1 antibody (Anti-Scl-70) not reactive, Anti-Smith antibody (Anti-SM) not reactive, Complement C3 and Complement C4 within normal limits.

An echocardiogram, Holter monitoring, chest CT scan and PET-CT scan were also performed externally. The first examination showed a Left Ventricular Ejection Fraction (LVEF) of 64% with indirect signs of pulmonary hypertension, as well as left ventricular diastolic dysfunction with altered relaxation and the presence of a slight pericardial effusion. The second examination showed no ventricular ectopic activity,

sporadic and repetitive supraventricular ectopic activity and no clinical-electrocardiographic correlation. The CT scan showed peripheral pulmonary opacities predominating in the lower lobes and the upper lobe of the left lung, associated with ground-glass opacities and thickening of the interlobular septa, which may be associated with an inflammatory process.

There was a solid pulmonary nodule, with regular contours, in the anterior basal segment of the left lower lobe, next to the oblique fissure, which was non-specific. The examination also showed the presence of moderate pericardial effusion, multiple lymph nodes and axillary and mediastinal lymph node enlargement in the upper and lower para-aortic and paratracheal chains, which were indeterminate. Another finding was the presence of a bone hemangioma in the vertebral body.

Finally, an external PET-CT scan was carried out. In relation to the metabolic findings of the exam, cervical lymph nodes were found in chains IIA, IIB and III, right supraclavicular, subpectoral and axillary, upper and lower paratracheal, perihilar lung region bilaterally, distal end of the esophagus and retroperitoneal (interaortocaval and pericaval). The findings without metabolic expression showed opacities and ground glass scattered throughout both lungs, bilateral fibroatelectatic bands, small nodule with soft tissue density and regular contours, measuring 0.6 cm, a small pericardial effusion, hepatomegaly, a mild degenerative process in the cervical, dorsal and lumbar spine and a hemangioma at T5.

The diagnostic impression of the first PET-CT scan was the presence of glycolytic hypermetabolism in the lymph node chains described, with the first diagnostic hypothesis being active lymphoproliferative disease. Due to her clinical condition and the results of the tests, especially the PET-CT, the patient was referred to the hospital and requested to be admitted for diagnostic investigation of probable lymphoma.

Because the patient presented features of SLE (lymphadenopathy, pericardial effusion, lymphopenia, positive direct coombs), SS (microstomia, sclerodactyly, insterstitial lung disease) and Polymyositis (muscle weakness, elevated CPK, aldolase, AST, lactate dehydrogenase), the hypothesis of lymphoma began to be questioned, with greater emphasis on a possible diagnosis of Mixed Connective Tissue Disease.

During her first hospitalization, new tests were carried out to better investigate the clinical case. Laboratory tests in the hospital showed: uric acid at 4.6 mg/dl, total calcium 7.4 mg/dl, urine test results were without alterations, negative serologies, high ferritin (1010 ng/mL), C-reactive protein 66 mg/L, magnesium 1.9 mg/dl, urea 16 mg/dl, creatinine 0.3 mg/dl, aspartate transaminase (AST) 96 U/L, alanine transaminase (ALT) 30 U/L, creatine phosphokinase (CPK) high (797 U/L), sodium 142mEq/L, potassium 4.3mEq/L, lactate dehydrogenase high (960 U/L), total proteins 7.8 g/dl, albumin 3.1 g/dl, prothrombin time (PT) 15 seconds, international normalized ratio (INR) 1.21, activated partial thromboplastin time (APTT) 51.4; blood count with leukopenia (approximately 6,000 leukocytes) with normal platelets, reticulocytes 0.4%, direct Coombs strongly positive (3+/4+), FAN reagent at 1/640 with fine dotted cytoplasmic pattern and fine dotted nuclear pattern; Anti-SSA negative and Anti-SSB positive (111.2); Rheumatoid factor reagent and Anti-RNP positive with a result of 157.2 (the latter test was carried out using the Elisa method, as the service in question does not use the hemagglutination method).

Electrocardiogram showed sinus rhythm with low diffuse amplitude. Chest X-ray showed significant cardiomegaly without the presence of consolidations. Computed tomography of the chest showed moderate to significant pericardial effusion, with discreet fibrosis predominantly at the lung bases without consolidations suggestive of infection. A cervical lymph node was biopsied. Macroscopy showed a nodular structure, compatible with a lymph node measuring 1.0 x 0.5 x 0.3 centimeters, brownish and elastic. The sections have a compact surface, with the same appearance as the outside.

Microscopically, the histological sections show a small lymph node with a distorted general architecture due to the absence of follicles. Lymphocytes of varying sizes, histiocytes and occasional eosinophils are observed, requiring immunohistochemical study to better characterize the diagnosis. An immunohistochemical study of the cervical lymph node assessed the presence or absence of nine antibodies in the sample. Of the nine, eight were positive (CD3, CD20, CD30, Bcl6, Bcl2, CD5, CD23 and Ki-67). The only negative antibody was Cyclin D1. In conclusion, the associated morphological findings do not support the hypothesis of neoplasia in the

sample in question, suggesting reactional lymph node enlargement. Thus, thanks to the patient's physical examination, the results of complementary tests and the report of the excisional lymph node biopsy associated with an immunohistochemical study, the diagnosis of Mixed Connective Tissue Disease was established and treatment for the disease was started.

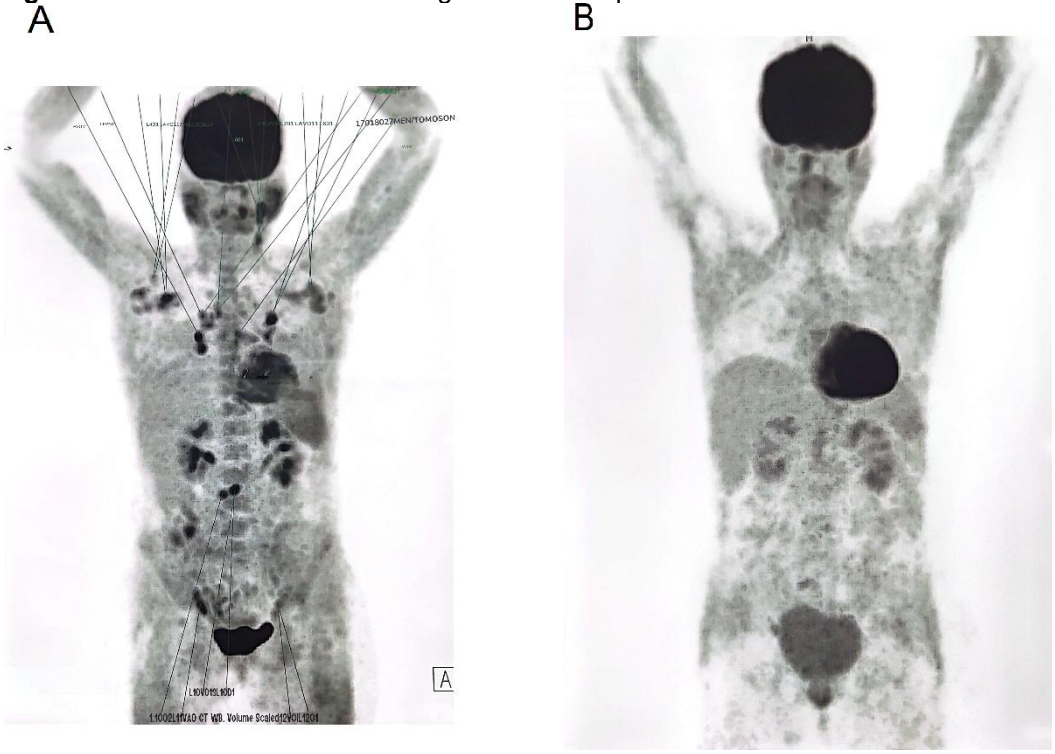
Three days of pulse therapy with methylprednisolone with1g/day, followed by prednisone 1mg/kg and a cyclophosphamide dose of 750mg, showed improvement in the initial condition in the weeks following the first hospitalization. After initial treatment, she was progressively weaned off prednisone and hospitalized monthly with cyclophosphamide for six months. After six months of treatment proposed by a rheumatologist and with significant clinical improvement, the patient underwent a new PET-CT scan for reassessment (**Figure 2**).

In relation to the findings with metabolic expression, the study, compared to the previous one carried out six months ago, showed a resolution of glycolytic hypermetabolism and a significant reduction in the dimensions of the cervical, thoracic, abdominal and pelvic lymph nodes and lymph nodes enlargement, in addition to the current study showing a physiological distribution of the radiopharmaceutical in the body segments analyzed. In relation to the findings without metabolic expression, the study showed:

Ground-glass opacities scattered throughout both lungs, notably in the lower lobes, with bilateral and residual fibroatelectatic bands; presence of prominent axillary and splenic lymph nodes, measuring up to 1.5 cm, without significant glycolytic metabolism (smaller compared to the previous study; small nodule with soft tissue density and regular contours, measuring 0.6 cm, adjacent to the left oblique fissure; slight pericardial thickening (resolution of the effusion); enlarged liver with regular contours and preserved density; spleen with preserved morphology and density, showing normal glycolytic metabolism and reduced dimensions compared to the previous study; degenerative changes in the spine; calcified granuloma in the subcutaneous tissue of the left gluteal region; hemangioma in the vertebral body of T5.

Figure 1 compares the two PET-CT scans carried out on the patient. **Figure 1A** shows the first scan carried out before treatment and showing high diffuse uptake in limph nodes. **Figure 1B** shows the second scan carried out after treatment, with a significant reduction in the uptake found previously.

Figura 1 - PET-CT scans taken during case follow-up.



Source: Bagio TM, et al., 2025.

DISCUSSION

First described in the early 1970s, MCTD has characteristics typical of other well-established autoimmune diseases, such as SLE, SS and poliomyositis, with the presence of antibodies against extractable nucleus antigens (ENA) being its main differentiating factor. A long time later, it was proven that the antibody target was anti-RNP, with the most affected particle being U1-RNP (SHARP GC, et al., 1972; FRANCO AS e MIOSSI R, 2022; SATO F, et al., 2023). Pulmonary involvement is very common in MCTD and is observed in up to 75% of cases. Interstitial lung disease and pulmonary hypertension are the most common pulmonary manifestations (SULLIVAN WD, et al., 1984; SANTACRUZ JC, et al., 2023).

Regarding the most common cardiovascular manifestations in this condition, most studies report that the main ones are pericarditis, myocarditis, mitral valve prolapse and left ventricular hypertrophy (LASH AD, et al., 1986; BURDT MA, et al., 1999; HAJAS A, et al., 2013; BERGER SG, et al., 2023). In 2019, Tanaka Y, et al. (2021), published the most recent and accepted criteria for diagnosing the disease.

The composition remained the same as the previous criteria: common manifestations, immunological criteria (presence of positive Anti-U1 RNP regardless of the method), typical manifestations and characteristics of the 3 poles that make up MCTD (SLE: polyarthritis, lymphadenopathy, malar erythema, pericarditis/pleuritis, leuko or thrombocytopenia; SS: sclerodactyly, interstitial lung disease, esophagealdysmotility or dilatation; and inflammatory myopathy: muscle weakness, elevated muscle enzymes and changes in electroneuromyography) (TANAKA Y, et al., 2021).

In our case, the diagnosis of MCTD was established by the Tanaka criteria. The patient had common manifestations (Raynaud's phenomenon, sclerodactyly), immunological criteria (positive Anti-RNP by ELISA method), typical manifestations (signs of pulmonary artery hypertension by echocardiogram) and characteristics of the three diseases that make up MTCD (SLE: lymphadenopathy, pericarditis, leukopenia; SSc: sclerodactyly, interstitial lung disease; Polymyositis: muscle weakness and elevated muscle enzymes) (TANAKA Y, et al., 2021).

The diagnosis of MCTD was not established by the other criteria consolidated in the literature because they use hemagglutination as the standard method for identifying the anti-RNP antibody, an old method that is not used by the referral service at the patient's hospital. In the past, anti-RNP was detected by immunodiffusion or counterimmunoelectrophoresis on agarose gels. These methods were considered insensitive for detecting autoantibodies, and it is difficult to use immunodiffusion to quantify antibody levels (TAN EM and KUNKEL HG, 1966; KURATA N and TAN EM, 1976).

Most clinical laboratories use solid-phase assays such as enzyme-linked immunosorbent assay (ELISA) to detect these autoantibodies (HOUTMAN PM, et al., 1986). Both double immunodiffusion and ELISA can be used to detect anti-RNP (TANAKA Y, et al., 2021). The result found on the PET-CT scan has so far been unique in the medical literature. We havenot found any similar clinical cases, where the MCTD mimicked a lymphoma.

This demonstrates the importance of a detailed rheumatological history and physical examination, given the increasingly common situation of patients with altered complementary tests, which can lead medical professionals to order unnecessary tests, exposing patients to risk and delaying proper diagnosis and treatment.

As a rare diagnosis, MTCD still generates controversy in medical literature worldwide. Alves and Isenberg. carried out a review highlighting some points of questioning about the disease: the presence of the same antibody in other autoimmune diseases, the presence of antibodies typical of other diseases that can appear in CTCD; and the preference for one of the three diseases during clinical evolution (“overlap” syndrome). Nimelstein et al. questioned the relevance of anti-U1-RNP for the diagnosis of MTCD, since the same antibody is also present in other rheumatological diseases, such as SLE (ALVES MR and ISENBERG DA, 2020).

The treatment of MTCD is not widely discussed in the literature and more studies are needed to better elucidate its therapy. Cappelli S, et al. (2012), treated patients with MTCD over a ten-year interval and obtained the following results: 58% were treated with immunosuppressants, 82% used glucocorticoids (regardless of

dose) and 45% used antimalarials. It is therefore understood that most cases of CKD are currently treated with immunosuppressive therapy associated with corticosteroids (CAPPELLI S, et al., 2012; ALVES MR and ISENBERG DA, 2020).

Hajas A, et al. (2013), evaluated 280 patients diagnosed with MTCD over a 32-year period in Hungary. Of this total, 219 used high-dose methylprednisone, 209 cytotoxic agents such as cyclophosphamide, azathioprine and methotrexate (most participants used combined therapy between pulse therapy and immunosuppressants, as used in the clinical case described) and only 42 patients used anti-TNF immunobiologicals (HAJAS A, et al., 2013; ALVES MR e ISENBERG DA, 2020).

Therefore, MCTD is a rare, complex and difficult-to-diagnose disease that includes various criteria, from clinical to laboratory. This case report made a scientific contribution, as it described a case of MCTD diagnosed using the most recent and modern criteria accepted for the disease, as well as proving, in an unprecedented way, that it can make a differential diagnosis with lymphoma, mimicking the neoplasm on PET-CT, strongly emphasizing the importance of anamnese and physical examination in the correct interpretation of complementary tests requested by health professionals to manage their patients.

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