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Case Report

Generalised Lymphadenopathy as the first manifestation of Systemic Lupus Erythematosus; Differential Diagnosis of Lymphoproliferative Disease. A Report☆

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A B S T R A C T

Generalised lymphadenopathy is a common manifestation, but usually non-specific and indicative of multiple diseases. Autoimmune diseases, including lupus erythematosus, may be the first manifestation of this finding, and therefore should be considered for differential diagnosis. In the cases presented, clinically and radiologically disseminated lymphadenopathy, they were confounding variables for rapid diagnosis, which is reached through the proper clinical and para-clinical context and with histopathological confirmation. Given that lupus is a potentially fatal disease, it is important to recognise this presentation.

Linfadenopatías generalizadas como primera manifestación de lupus eritematoso sistémico; un diagnóstico diferencial de enfermedad linfoproliferativa. Un reporte de dos casos

Palabras clave:
Linfadenopatías
Lupus eritematoso sistémico
Diagnóstico

R E S U M E N

Las adenopatías generalizadas son una manifestación frecuente, aunque usualmente inespecífica e indicativa de múltiples enfermedades. Las enfermedades autoinmunes, entre ellas el lupus eritematoso sistémico, pueden tener como primera manifestación dicho hallazgo; por lo tanto se deben tener en cuenta para el diagnóstico diferencial. En los casos que se presentan, las adenopatías diseminadas encontradas clínica y radiológicamente, fueron una variable de confusión para el diagnóstico rápido y al que se logró llegar mediante el adecuado contexto clínico, paraclínico y el estudio histopatológico. Dado que el lupus es una enfermedad potencialmente fatal, es importante reconocer esta forma de presentación.

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Introduction

The lymph nodes are conglomerates of cells that are part of the defense system; of which more than 600 have been recognised[1]; when there is an abnormality in the size or in the nature of the nodes, they are called lymphadenopathies.[2] Lymphadenopathies may be due to multiple conditions that can be easily remembered with the acronym "MIAMI" (Malignancy, Infections, Autoimmunity, Miscellaneous, Iatrogenic)[2]; this clinical manifestation may constitute a diagnostic challenge for the clinician, since in some occasions the broad differential makes difficult a clear and early etiological approach.

Systemic erythematosus lupus (SLE) is a potentially fatal autoimmune disease that in many occasions is confused with other conditions; with an estimated prevalence of approximately 40 cases per 100,000 people.[3] The frequency of occurrence of lymphadenopathies in SLE is variable, being reported a range between 25% to 50%,[4] and they are associated with different clinical and paraclinical characteristics of disease activity such as malar erythema, oral ulcers, splenomegaly, alopecia, and positivity of anti-double stranded DNA, among others.[5]

Below we present two clinical cases of patients who consulted with generalised lymphadenopathy as the cardinal symptom, in which because of the form of presentation, the first differential diagnosis was the lymphoproliferative diseases; however, an exhaustive interrogation and a rational clinical approach led to the accurate diagnosis of SLE, allowing for an adequate treatment.

Presentation of the Cases

Case 1

A 23 year-old female patient from Ibague, who consulted in March 2012, because of a clinical picture of three months of evolution, consisting of weight loss of approximately 20 kg, associated with night sweats, asthenia, adynamia, joint pain predominantly in hands and shoulders, accompanied by loss of muscle strength in the lower limbs, alopecia and predominantly nocturnal fever.

As medical history she had hypothyroidism and received thyroid hormone replacement therapy. Axillary lymphadenopathies were found on the physical examination and therefore, extension studies were initiated with the suspicion of lymphoproliferative syndrome *versus* lymph node tuberculosis. A biopsy of a left axillary node was taken with a pathology report of lymphoproliferative disease suggestive of a reactive process, characterized by fused follicles of different sizes, preservation of the mantle and active germinal centers.

With these findings the patient consulted to our institution, where she was hospitalized and extension studies were initiated. On physical examination drew attention the presence of right cervical lymphadenopathies, bilateral inguinal lymphadenopathies, and abdomen with hepatomegaly. The computed axial tomography (CT scan) of the neck reported multiple bilateral subcentimetric lymph nodes; the chest CT scan described axillary adenomegalies, and the abdominal-pelvic CT scan showed retroperitoneal adenomegalies (Figs. 1-3). Paraclinical tests were requested to rule out infectious processes (Table 1).

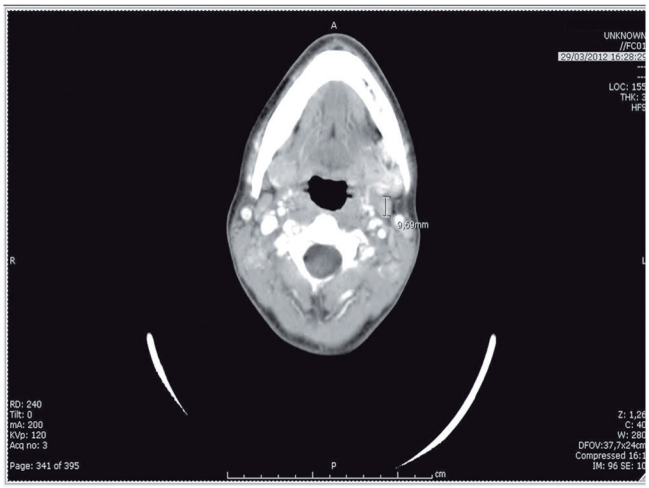

Figure 1 – Cervical TC scan: there are multiple bilateral subcentimetric adenomegalies.

It was indicated to take an excisional biopsy along with an immunohistochemical study of a left axillary node, which showed morphological and immunophenotypical findings that corresponded to florid reactive follicular hyperplasia; there was no evidence of neoplastic commitment or formation of granulomas.

With these results, the patient was reevaluated considering constitutional syndrome, B symptoms associated with arthralgia of more than 3 groups of joints, alopecia, Raynaud's phenomenon (detected in the new interrogation); hemogram with bicytopenia (leukopenia and heterogeneous hypochromic microcytic anemia) and strongly positive anti-double stranded DNA. In view of the foregoing, a diagnosis of SLE was made, and then commenced deworming, methylprednisolone bolus and hydroxychloroquine.

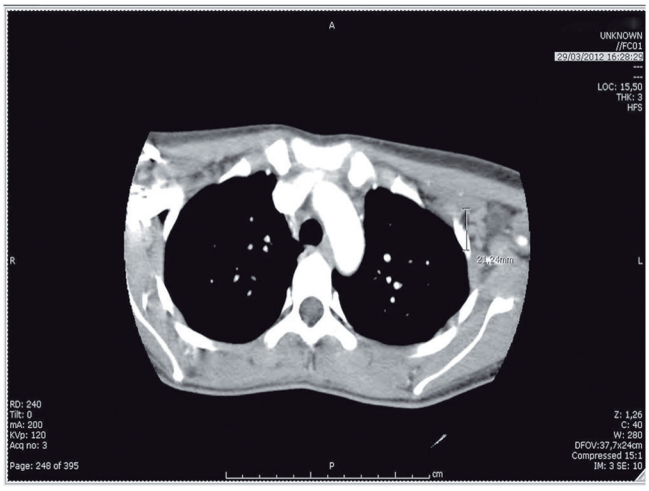

Figure 2 – Chest CT scan showing axillary adenomegalies compatible with lymphoproliferative disease.

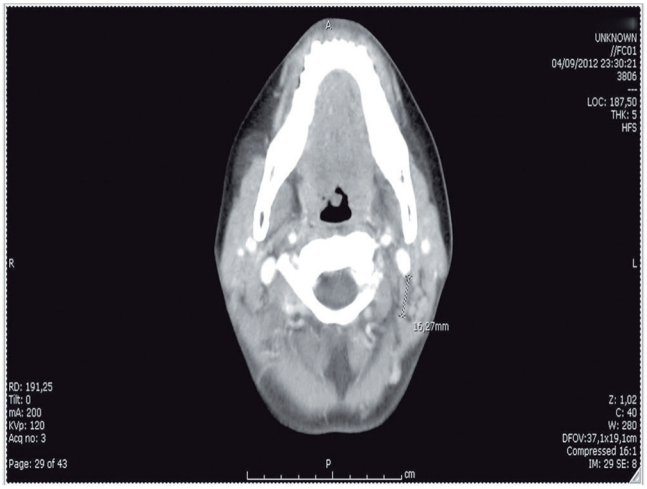

Figure 3 – CT scan of abdomen and pelvis: retroperitoneal adenomegalies.

Case 2

A 15-year old female patient from Bogota, high-school student, who consulted because of a clinical picture of 2 months of evolution, consistent of generalised osteomyalgia, dorsolumbalgia, joint pain predominantly in the hands, knees and feet, with subsequent walking limitation due to the pain and secondary prostration; she also had lost 10 kg in the last 4 months, and had hair loss and fever of 15 days of evolution.

She had been extra-institutionally hospitalized, with clinical findings of generalised lymphadenopathies associated with leukocytosis, and it was decided to perform a bone marrow biopsy which was within normal limits.

The patient was admitted to the hospital due to exacerbation of the described symptomatology and on the physical examination she was alert, oriented, tachycardic, afebrile, normotensive, with generalised mucocutaneous paleness, right conglomerate preauricular lymphadenopathies, movable painless cervical lymphadenopathies, and decreased muscle strength in lower limbs with hypotrophy of the extremities.

With the described clinical findings, SLE was suspected and extension studies were started (Table 2). There were requested a CT scan of the neck, which reported bilateral adenomegalies of right predominance; a chest CT scan which reported local fibroatelectatic tract and loss of volume with laminar pleural effusion and bilateral axillary adenomegalies, and an abdominal CT scan which described para-aortic lymph nodes (Figs. 4-7).

Table 1 – Laboratory Report of the Patient of Case 1

Laboratory	Result
Leukocytes	3,400 cells/mm^3
Neutrophils	2,300 cells/mm^3
Lymphocytes	800 cells/mm^3
Hemoglobin	10.3 g/dl
MCV	77.9 fl
MCH	25.6 pg
Platelets	381,000
PT	10.6 CD 11.3
PTT	31.2 CD 15.5
Inhibition test	Negative
Russell's viper venom test	Negative
RCP	1.6 mg/dl
VDRL	Negative
Creatinine	0.5 mg/dl
AST	31 U/L
ALT	27 U/L
CMV	Positive IgG (42), negative IgM
Hepatitis B, C, HIV	Negative
EBV	Negative
TSH	6.99 uIU/ml (RV 0.4 to 4.6)
FT4	15.7 (RV 10-28)
Anti-DNA	1005 (strongly positive).
Rheumatoid factor	Negative
C3	25 (RV 90-180)
C4	2.9 (RV 10-40)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CMV: cytomegalovirus; C3: complement component 3; C4: complement component 4; DNA: deoxyribonucleic acid; MCH: mean corpuscular hemoglobin; RCP: reactive C protein; PT: prothrombin time; PTT: partial thromboplastin time; TSH: thyroid stimulating hormone; FT4: free thyroxine; MCV: mean corpuscular volume; VDRL: venereal disease research laboratory; EBV: Epstein-Barr virus; HIV: human immunodeficiency virus.

Table 2 – Laboratory Report of the Patient of Case 2

Laboratories	Results
Leukocytes	3,900 cells/mm^3
Neutrophils	2,700 cells/mm^3
Lymphocytes	1,000 cells/mm^3
Hemoglobin	8.8 g/dl
Hematocrit	27%
MCV	81.4 fl
MCH	26.6 pg
Platelets	263,000
PT	10.5 CD 10.4
PTT	20 CD 31.7
RCP	5.7 mg/dl
Creatinine	0.7 mg/dl
AST	42 U/L
ALT	27 U/L
C3	Lower than 40 (RV 88-165)
C4	Lower than 8 (RV 14-44)
ANA	Positive speckled pattern
Anti-double stranded DNA	1,600 UI/ml (strongly positive)
Anti-Sm	12.7 (negative)
Anti-SCL 70	7.6 (negative)
Serum iron	16 (RV 37-181)
Transferrin	147
Ferritin	369 (RV 6.24-137)
Hepatitis B, C, HIV	Negative
TSH	6.56 (RV 0.4-4.68)
FT4	23.4 (RV 10-28)
Toxoplasma IgG and IgM	Negative

ALT: alanine aminotransferase; ANA: antinuclear antibodies; Anti-SCL 70: anti-topoisomerase 1 antibodies; Anti-Sm: anti-Smith antibodies; AST: aspartate aminotransferase; C3: complement component 3; C4: complement component 4; DNA: deoxyribonucleic acid; MCH: mean corpuscular hemoglobin; RCP: reactive C protein; PTT: partial thromboplastin time; PT: prothrombin time; TSH: thyroid stimulating hormone; FT4: free thyroxine; MCV: mean corpuscular volume; HIV: human immunodeficiency virus.

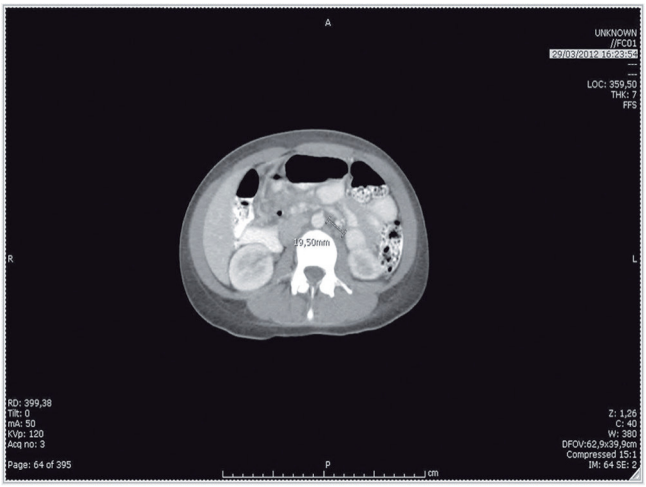

Figure 4 – Cervical CT scan: bilateral adenomegalies of right predominance.

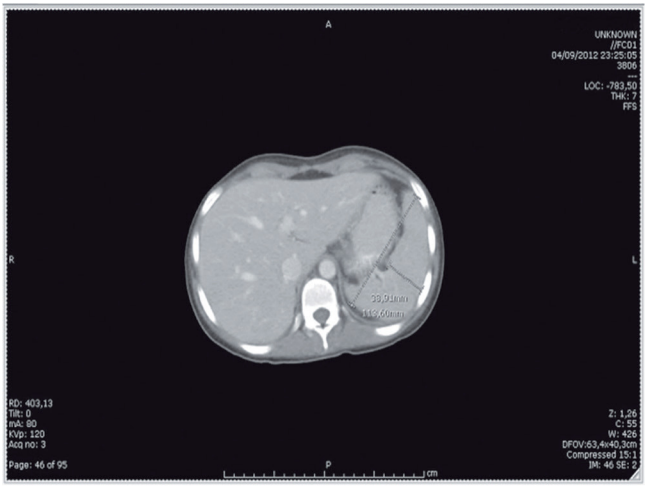

Figure 6 – Abdominal CT scan: hepatosplenomegaly.

With these findings, it was made a diagnosis of SLE and it was decided to start the management with pulses of methylprednisolone, presenting significant improvement in the clinical status on the third day.

Discussion

In the present study are reported two clinical cases of patients with generalised lymphadenopathy that because of their form of presentation, led to the initial diagnosis of neoplasm of lymphoproliferative type; however, the histological findings and the thorough evaluation of the anamnesis led to the accurate diagnosis of SLE, with the consequent improvement once the targeted management was started.

The differential diagnosis of neoplastic hematological disease, in these patients, is logical given the presence of constitutional symptoms and recognizing that in up to 80% of lymphomas there are lymphadenopathies in the course of the disease.[6] In addition, the risk of concomitance between the two conditions is known, being reported in the literature an association with SLE and other autoimmune conditions such as thyroiditis, Sjögren's syndrome, among others.[7] Landgren et al., in a Scandinavian case-control study concluded that there is a strong correspondence between SLE and Hodgkin's lymphoma with an odds ratio of 5.8 (CI of 2.2-15.1),[8] as well as a higher frequency of Castleman's disease in this group of patients.[9] Apora et al., in a meta-analysis of prospective cohorts describe an increased risk of Hodgkin's lymphoma, non-Hodgkin lymphoma, leukemia and myeloma when compared with the general population.[10]

Persistent lymphadenopathies in patients with SLE who do not respond to treatment may be indicative of lymphoma, as commented previously. Several studies conducted since 1970

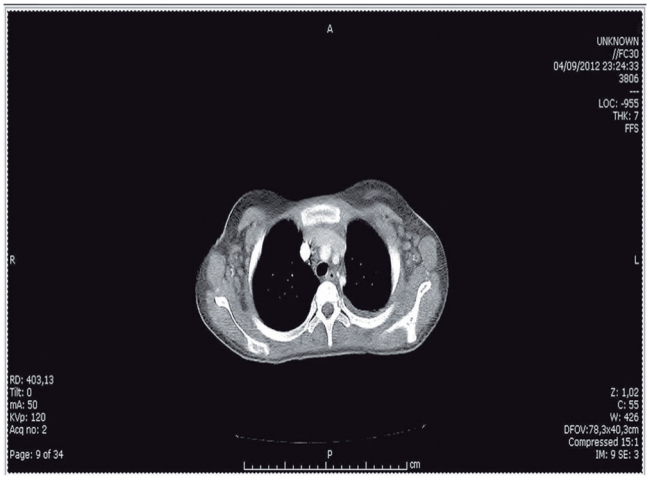

Figure 5 – Chest CT scan: local fibroatelectatic tract and loss of volume, laminar pleural effusion and bilateral axillary adenomegalies.

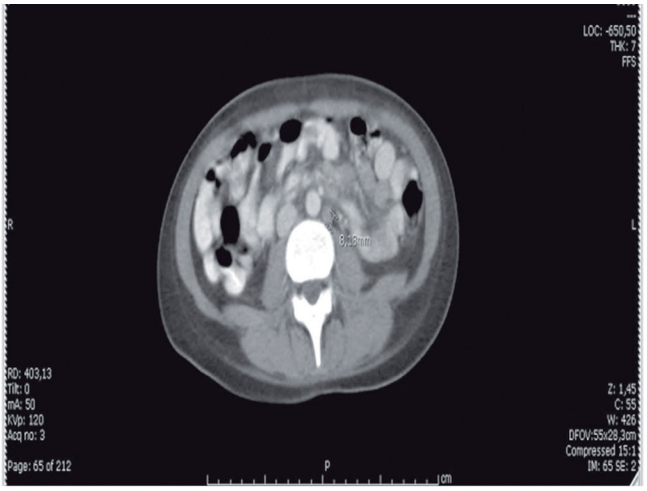

Figure 7 – Abdominal CT scan, para-aortic lymphadenopathies.

have reported an increased risk of malignancy in autoimmune diseases; this risk is secondary to the combination of mutations in germ and somatic lines, persistent immune overstimulation and pharmacological immunosuppression.[11,12]

These reasons support the fact that the biopsy of the lymphadenopathies plays an important role when the clinical suspicion deserves it or when the patient has a previous diagnosis of SLE and the lymphadenopathies do not improve despite a proper management. The association between the activity of the autoimmune disease and the increased risk of these neoplasms is contradictory, given the findings of different observational studies.[13]

Among the autoimmune diseases, SLE is a relevant condition since it is potentially fatal and it can be easily confused with many other disorders. The prevalence of lupus is approximately 40 cases per 100,000 people in Northern Europe, and in the United States the number of patients with lupus exceeds 250,000.[3] The lymphadenopathies associated with SLE, in the majority of cases, are localized and in few occasions they appear as generalised lymphadenopathies at the beginning of the disease; in addition, in the validation of the latest classification criteria they are excluded as a diagnostic element.[14] With these two cases reported we evidence that this form of presentation may occur and is important to consider it in the differential diagnosis.

Age is related with the form of presentation of SLE and lymphadenopathies are not outside of this characteristic, being more frequent when the disease appears at an early age.[15] In a meta-analysis, Livingston et al. reported findings consistent with previous publications, an OR of 3.67 (CI 1.18 to 11.45) for the presence of lymphadenopathies when SLE begins in the youth.[16]

In the cases in which the lymphadenopathy occurs as the primary manifestation of lupus, is almost always accompanied by additional constitutional symptoms, especially in young patients[17] and its presence has been associated with increased activity of the disease. Other findings observed in this form of presentation are fatigue, fever, weight loss, skin lesions, hepatomegaly, splenomegaly, increased anti-DNA antibodies, and decreased levels of complement.[5]

The lymph nodes are typically tender, painless, of variable size ranging between 0.5 and 3-4 cm and they appear most frequently at the cervical, axillary and inguinal levels.[4] During the remission of the disease the lymphadenopathies tend to disappear; however, in some patients they diminish in size and can be persistently localized.

The histological findings are usually non-specific and they consist of moderate follicular hyperplasia associated with increased vascularity or foci of necrosis with blastoid cells, remnants of karyorrhexis, macrophages and histiocytes.[18] In lupus, the lymphadenopathies are a benign finding and they can be seen at any stage of the disease; this appearance in the biopsy is not specific to any diagnosis and it can occur in a great variety of conditions, including viral infections and other autoimmune diseases.[19] Hematoxylin bodies are considered characteristic of lupus lymphadenopathies but they are not always found.[18,20] The biopsy might be performed with fine needle, however, it requires the assessment by an experienced pathologist; otherwise, it would be better an excisional biopsy and study with colorations and immunohistochemistry, since the diagnosis of lymphoma cannot be initially excluded.[12]

Other conditions with autoimmune substrate, such as rheumatoid arthritis, Sjögren's syndrome, sarcoidosis and Still's disease should be ruled out as differential diagnosis.[1]

The great majority of infectious diseases can manifest themselves with regional or disseminated lymphadenopathy; those that most frequently generate this finding are bacterial infections, infection with the human immunodeficiency virus, cytomegalovirus, tuberculosis, infection with the Epstein-Barr virus and toxoplasmosis.[21] There are other non-neoplastic or infectious diseases that generate lymphadenopathies, including the reactive lymphoid hyperplasia, dermatopathic lymphadenitis, Rosai-Dorfman's disease, Kimura's disease, Kikuchi-Fujimoto disease and lymphadenopathies associated with autoimmune and metabolic disorders; therefore, an adequate approach of the patient who is admitted with this clinical syndrome obliges to rule out these conditions or others[22] that are listed in Table 3.[2]

Another condition, not less important, is Kikuchi's lymphadenitis, also known as necrotizing lymphadenitis, which is a benign syndrome of unknown cause that occurs mainly in young adults who have lymphadenopathies and fever. The lymphadenopathy is typically limited to the cervical nodes and in rare cases there is generalised lymphadenopathy. Cutaneous manifestations have been described in up to 40%

Table 3 – Causes of Lymphadenopathies. Acronym "MIAMI"

Malignancy	Infections	Autoimmune	Miscellaneous	Iatrogenic
Lymphomas	Brucellosis	SLE	Kawasaki disease	Serum sickness
Leukemias	Cat-scratch disease	Rheumatoid arthritis	Sarcoidosis	Drugs
Skin neoplasms	Cytomegalovirus	Sjögren's syndrome		
Kaposi's sarcoma	Infectious mononucleosis			
Metastasis	Lymphogranuloma venereum			
	Pharyngitis			
	Rubella			
	Tularemia			
	Typhoid fever			
	Syphilis			
	Viral hepatitis			

Adapted and modified from Bazemore et al.[2]

of cases. The pathological examination of the lymph nodes reveals a characteristic pattern of necrotizing lymphadenitis. The resolution of this lymphadenitis occurs spontaneously and usually a few weeks after the onset of the symptoms.[23] In some occasions it is a diagnostic challenge since it can simulate SLE with hematologic involvement or it can occur simultaneously with it, thus generating a difficulty in the characterization and diagnosis.[24]

Conclusion

Generalised lymphadenopathy is a common clinical condition, which demands an exhaustive analysis of all the elements of the clinical history in order to reach a reasonable and logical approach.

Even though the lymphadenopathies are not the most frequent manifestation of SLE and they are not included in the latest classification criteria, they must always be taken into account within the broad differential diagnosis, since an opportune diagnosis allows offering the patient an early management. Under these conditions the probability of concomitance with other diseases that require an additional management cannot be disregarded; so the clinical judgment and an integration of the clinical, pathological and radiological findings are essential to reach an adequate diagnosis.

Ethical Disclosures

Protection of people and animals. The authors declare that no experiments were performed on human beings or animals for this research.

Data confidentiality. The authors declare that they have followed the protocols of their workplace on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the informed consent from the patients and/or subjects referred in the article. This document is held in the possession of the corresponding author.

Conflict of Interest

The authors declare that they have no conflict of interest.

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