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Chapter

Granulomatous Diseases Mimicking Sarcoidosis

Angel Robles-Marhuenda

Abstract

Granulomatous diseases are not infrequent in daily clinical practice. Granulomas are the expression of a sufficiently (partial) functioning immune system. Many diseases, with different etiologies (infection, autoimmunity, inflammatory, foreign bodies, malignancy, metabolites, chemicals, etc.) can cause granulomatous manifestations. The differential diagnostic process of a granulomatous disease should always be made in an interdisciplinary cooperation. Diagnostic procedures should be oriented to the clinical symptoms suggestive microbiological studies, and radiography but the diagnosis of a granulomatous disease should always be confirmed by histopathology when possible, sampling for histology or cytology. From a pathogenic point of view, they are divided into noninfectious and infectious granulomas. In the case of proven granulomatous inflammation, an infectious etiology should first be excluded (including mycobacteria, parasites, and fungi). From a clinical point of view, it is useful to separate granulomatosis into localized and disseminated forms, although this distinction can be sometimes artificial. Three types of localized granulomatous lesions can be distinguished: infectious granulomas, palisaded granulomas (granuloma annulare, necrobiosis lipoidica, and rheumatoid nodules), and foreign body granulomas. Disseminated granulomas can be divided into infectious, in particular tuberculosis, and noninfectious forms (autoimmune, neoplasia, etc.).

Keywords: granuloma, immune system, infection, inflammation, immunodeficiency

1. Introduction

Granulomatous diseases are not uncommon in daily clinical practice. Different etiologies (infection, autoimmunity, inflammation, foreign bodies, malignancy, metabolites, chemicals, etc.) can cause granulomatous lesions.

The differential diagnostic process for a granulomatous disease should always be made in light of interdisciplinary cooperation as it requires close collaboration between specialists including radiologists, internists, and pathologists.

Diagnostic procedures should be oriented to the clinical symptoms and should include blood analyses (liver and renal function control check, etc.), suggestive microbiological studies, and radiography (especially computed tomography or magnetic resonance imaging or positron emission tomography); the diagnosis of a granulomatous disease should always be confirmed by histopathology when possible, sampling for histology or cytology.

From a pathologic point of view, the lesions are divided into noninfectious and infectious granulomas. In the case of proven granulomatous inflammation, an infectious etiology (including mycobacteria, parasites, and fungi) should first be excluded.

From a clinical point of view, it is useful to separate granulomatosis into localized and disseminated forms, although this distinction can be sometimes artificial. Three types of localized granulomatous lesions can be distinguished: infectious granulomas, which are generally associated with localized infections, palisaded granulomas (granuloma annulare, necrobiosis lipoidica, and rheumatoid nodules), and foreign body granulomas. Disseminated granulomas can be divided into infectious (in particular tuberculosis) and noninfectious forms (autoimmune, neoplasia, etc.). These entities are discussed herein.

Granulomatous disorders are a heterogeneous group of diseases, the pathophysiological mechanism of which is still poorly understood. These are granulomatous inflammatory reactions to a wide variety of stimuli, including infections, systemic inflammations, neoplasia, metabolic disorders, and chemicals.

A granuloma is a specific form of inflammation involving mostly dendritic cells, T lymphocytes, and macrophages, which are the dominant cell type. Both innate and adaptive immunity are involved in this inflammatory process. From a clinical point of view, it is useful to separate granulomatosis into localized and disseminated forms, although this distinction may sometimes be artificial, because they often coexist. These are most frequently seen as pulmonary, hepatobiliary-splenic, gastrointestinal, renal, cerebral, and bone granulomas. From a pathogenic point of view, they are divided into noninfectious and infectious granulomas. Treatment is specific for each type.

2. Cutaneous localizad granulomatosis

The typical macroscopic skin lesion of cutaneous granulomatosis is characterized by an infiltrated painless rounded papule, which is well limited and reddish-pink and takes a yellowish color on diascopy, called apple jelly. Its surface is smooth or slightly squamous as there is generally no epidermal involvement [1].Three types of localized skin granulomatous lesions can be distinguished, namely, palisaded granulomas (like granuloma annulare, necrobiosis lipoidica, or rheumatoid nodules), infectious granulomas (which are generally associated with localized infections), and foreign body granulomas [1, 2].

2.1 Palisadic granulomas

This term corresponds to a histological description of a nodular inflammatory granulomatous lesion characterized by a central zone of altered connective tissue, surrounded by histiocytes dispersed in a palisaded form. The anomalies observed at the center of the granulomas generally make it possible to distinguish the different forms: mucin deposits in granuloma annulare, necrosis in necrobiosis lipoidica, and massive necrosis with fibrin deposits in rheumatoid nodules.

2.1.1 Granuloma annulare

This is the most commonly occurring form of cutaneous granulomas; two thirds of patients are under 30 years of age, with a male to female ratio of 2:1. Skin

involvement predominates in the extremities and rarely involves the face. The localized form is the more common (75% of the cases) than disseminated disease. Disseminated granuloma annulare has also been described, sometimes isolated and sometimes reported to be in association with several conditions (i.e., paraneoplastic forms associated with solid organ tumors or lymphoma). In these patients, the skin picture is often atypical [1]. The dermatological expression is in the form of erythematous plaques, grouped in rings with centrifugal progression. These plaques are themselves made up of small, firm, and well-defined papules. These lesions are asymptomatic and generally located on the back of the hands and feet, wrists, ankles, and dorsolateral faces of the fingers. In the disseminated form, it is arranged symmetrically, mainly on the trunk and the extremities. The diagnosis is clinical, the cutaneous biopsy being useful in doubtful cases. Sometimes the biopsy itself leads to a regression of the lesion. The evolution of these skin lesions is unpredictable but generally benign. Typically, the skin lesions disappear spontaneously within a few months to 2–3 years. Treatment is usually indicated when the lesions are very generalized.

2.1.2 Necrobiosis lipoidica

Necrobiosis lipoidica is an idiopathic chronic granulomatosis, which usually occurs in young or middle-aged adults, with a male to female ratio of 1:3. It is associated with diabetes mellitus, although its development is not related to poor glycemic control.

Necrobiosis refers to a histological inflammation triggered by cell death, and lipoidica refers to the clinically yellowish appearance of the lesions due to lipid deposits secondary to collagen degeneration. The lesions present as bilateral painless papules or nodules, which widen progressively and converge into well-defined oval plaques with a raised erythematous border surrounding the central area, which is initially reddish and later becomes yellowish, smooth, and atrophic with telangiectasias and scarring. Over time, the plaque becomes indurated and adherent to the underlying osteoperiosteal planes, with a remaining active border. Isolated cases of squamous cell carcinomas have been reported in patients with large lesions.

2.1.3 Rheumatoid nodules

Rheumatoid nodules are the most frequent extra-articular manifestations of rheumatoid arthritis (RA). At least 20% of adult patients with RA have rheumatoid nodules. Patients with rheumatoid nodules are more often rheumatoid factor and anti-cyclic citrullinated peptide positive. Their presence in newly diagnosed patients can be considered as a clinical predictor of severe seropositive and erosive arthritis associated with extra-articular involvement, including rheumatoid vasculitis. They consist of deep dermo-hypodermic nodules of variable size (2 mm to 5 cm) adherent to the periosteum. Generally painless, these nodules can cause discomfort or pain when they ulcerate. The nodules tend to develop in outbreaks during the active phases of the disease and form subcutaneously, in the bursas and along the tendinous sheaths. Although they have been described in almost all regions and can occur in the viscera (lung, liver), these nodules are typically located at pressure points, such as on the extensor surface of the arm, the Achilles tendon, the ischial area, and on the flexor surfaces of the fingers. These lesions may develop gradually or abruptly and are usually associated with some symptoms of inflammation. A biopsy

of the nodule may be necessary if the diagnosis is uncertain. Over time, rheumatoid nodules often disappear or regress, evolving sometimes, independent of treatment. Rheumatoid nodules appearing without clinical or biological rheumatic symptoms are most often deep granuloma annulare or pseudorheumatoid nodules, particularly in children and in the cephalic region [1, 2].

2.1.4 Lupus miliaris disseminatus faciei (acne agminata; necrotizing granulomatous rosacea)

Lupus miliaris disseminatus faciei is now believed to be a peculiar variant of rosacea. It presents with multiple reddish papules and nodules of the scalp and face, principally in young adults, and is centered on hair follicles, without pus formation. It usually persists for 2–3 years and then regresses, leaving residual scars [2].

2.2 Foreign body granulomas

Foreign body granulomas consist of an excessive cutaneous inflammatory response to any material in the dermis or subcutis (endogenous or exogenous). The clinical presentation and evolution depends on several factors: tissue response to the foreign body, anatomical site, penetration, composition, amount of material involved, quantity, and volume. They may appear as papules, nodules, or erythematous plaques which harden over time due to fibrosis. The time gap between entrance of the foreign body into the skin and appearance of granulomas is very variable, sometimes being as long as several years.

Among the endogenous substances, hair, calcifications, cholesterol crystals, or uric acid are common; while exogenous substances commonly include insects, silica (talc), beryllium, aluminum, or tattoo ink.

In recent years, the use of cosmetic materials and, in some cases, the implantation of medical material have been implicated in this regard. In recent years, a granulomatous and inflammatory systemic picture secondary to a foreign body reaction has been defined by diverse substances such as biomaterial injections and prostheses (mainly silicone, hyaluronic acid, acrylamides, and methacrylate compounds). The process is defined as autoimmune/inflammatory syndrome induced by adjuvants (ASIA) and is characterized by chronic fatigue, pyrexia, dry mouth, sleep disturbances, myalgia, myositis, muscle weakness, lymph nodes, arthralgia and/or arthritis, and foreign body-type granuloma, in the absence of any autoantibody, infection, or cancer. Symptoms may disappear after removal of the implant material [3].

2.3 Localized infectious granulomas

Infectious granulomas are usually chronic and localized skin infections, the agent being mycobacteria (tuberculosis or atypical mycobacteria), parasites (leishmaniasis), or fungi (cryptococcosis) in an immunocompromised host. With the exception of cutaneous leishmaniasis, granulomatous infections have to be considered as skin manifestations of systemic infections. They thus require systemic treatment directed toward the cause.

2.3.1 Cutaneous tuberculosis (TB)

Cutaneous tuberculosis (TB) accounts for less than 2% of all extrapulmonary tuberculosis manifestations and occurs in 10% of all patients with TB.

Skin manifestations of TB represent a clinical polymorphism that can be explained by various factors such as the pathogenicity of the bacterial strain, the immune status of the host, previous treatment, or local factors (i.e., proximity to lymph nodes). Localized forms include lupus vulgaris, a violaceous yellowish cutaneous plaque with serpiginous centrifugal extension, desquamation, and central atrophy, scrofuloderma (an erythemato-violaceous painless nodule, with suppuration as sign of per contiguitatem extension of ganglionic, osteoarticular), or epididymal tuberculosis or verrucous cutaneous tuberculosis (a keratotic plaque with irregular edges and dystrophic scarring on the skin of the hands). Cutaneous atypical mycobacteria infections have heterogeneous clinical appearance, including nodules, papules, plaques, pustules, abscess, and ulcers. *Mycobacterium marinum* is the most commonly involved strain. It causes skin and soft tissue infections after exposure to aquatic environments or marine animals ("tank granuloma"). Patients typically show clusters of nodules, ulcers, or verrucous plaques that may spread from the arms or legs in a sporotrichoid pattern. Mycobacterium chelonae is a rapidly growing mycobacterium that causes dark red nodules and, occasionally, abscesses. The infection is related to skin wounds due to penetration procedures (injection, liposuction, acupuncture, tattoos, etc.).

2.3.2 Cutaneous lesihmaniasis

Cutaneous leishmaniasis involves exposed body parts, causing nodules, ulcers, and scarring. Acute cutaneous leishmaniasis or East button is the most common form. The lesion, initially papular, rounded or oval, and asymptomatic or mildly pruritic, may be single or multiple and commonly located on the face or areas of uncovered skin. Gradually it takes a darker reddish tone while it infiltrates and increases in size. The surface is occasionally covered with furfuraceous scales and, in 1–3 months, is transformed into a nodular lesion or a deep infiltrated plaque. Chronic cutaneous leishmaniasis includes cases that exceed the duration of 1–2 years. The lesions are usually more polymorphic (large indurated plaques with papular borders, eczematiform, warty, keloidal, etc.), and the clinical difficulty of the diagnosis is due to the lower sensitivity of microscopic smear examination, the crops, and the histopathology.

2.4 Syndromic mucocutaneous granulomatous disorders

Cutaneous nonnecrotizing/necrobiotic granulomas may be part of syndromic complexes that include lesions in other organs and tissues as well. The two principal representatives of this group are the Melkersson-Rosenthal syndrome (orofacial mucocutaneous granulomatosis; cheilitis granulomatosa) and Blau syndrome [2].

The constituent signs of Melkersson-Rosenthal syndrome include the association of recurrent facial and/or lip edema, recurrent facial paralysis, and fissured tongue. It has been associated with Crohn's disease. Miescher's cheilitis granulomatous consists of the appearance of recurrent labial edema in one or both lips, which can be persistent. It has traditionally been considered as a monosymptomatic form of Melkersson-Rosenthal syndrome.

Blau syndrome is an autosomal-dominant autoinflammatory condition that includes granulomatous inflammation in the skin, together with granulomatous iridocyclitis and granulomatous arthritis with camptodactyly. It is related to mutations in the CARD15/NOD2 gene complex and may also have a linkage to Crohn's disease.

3. Systemic granulomatosis diseases

3.1 Infectious disseminated granuloma

Almost all infectious pathogens can induce granulomas (**Table 1**). Although the skin tends to be frequently affected, visceral involvement is usually coexisting, as is a systemic inflammatory process (fever, asthenia, etc.). There is no universal pattern of visceral or cutaneous involvement; the epidemiological and clinical context is essential, and physical history can provide data on the etiological agent.

Among infectious agents, mycobacteria are the most frequently involved. In tuberculosis and leprosy, there is either a true skin infection or tuberculids, which are regarded as a cutaneous hypersensitivity reaction to *Mycobacterium leprae* linked to the release of an antigen by an internal mycobacteria infectious focus. Skin tuberculid lesions are not contagious. The clinical manifestations of tuberculosis tuberculids are erythema nodosum, erythema induratum of Bazin, papulonecrotic tuberculids, lichen scrofulosorum, and lupus miliaris disseminatus faciei, whose differential diagnosis is granulomatous rosacea. Some agents have tropism due to specific viscera, such as bartonella due to the liver or the vascular affectation of syphilis. Some viruses are associated with specific vasculitic systemic processes, such as panarteritis nodosa in the case of hepatitis B or vasculitis cryoglobulinemia induced by the hepatitis C virus.

3.2 Noninfectious disseminated granuloma

There are many etiologies of noninfectious disseminated granulomas (**Table 2**). Possibly sarcoidosis is the prototype of these diseases, although it will not be

Bacteria	Virus	Fungi	Parasites
M. tuberculosis	Human immunodeficiency virus	*Candida* sp.	Toxoplasmosis
M. marinum	Epstein-Barr virus	*Aspergillus* sp.	*Leishmania* sp.
M. chelonae	Cytomegalovirus	Cryptococcosis	Bilharzia
M. avium (MAI)	Hepatitis B virus	Histoplasmosis	*Toxocara canis*
M. leprae	Hepatitis C virus	Blastomycosis	*Capillaria hepatica*
T. pallidum (syphilis)		Coccidioidomycosis	*Ascaris*
Salmonella sp.		Paracoccidioidomycosis	*Strongyloides*
Bartonella henselae		*Penicillium*	*Giardia lamblia*
Kleb. granulomatis (donovanosis)		*Sporothrix schenckii*	*Fasciola*
Listeriosis		*Pneumocystis jiroveci*	Schistosomiasis
Brucella			*Enterobius vermicularis* (pinworms)
Pasteurella			*Echinococcus granulosus*
Yersinia			*Echinococcus multilocularis*
Nocardia			
T. whipplei			
Rhodococcus equi			
Tularemia			
Melioidosis			
Coxiella burnetii			
Borrelia burgdorferi			

Table 1.
Common infectious diseases causing disseminated granulomatosis.

Immune-mediated inflammatory diseases

A. Organ specifies primarily

- Sarcoidosis
- Bronchogenic granulomatosis
- Inflammatory bowel disease
- Autoimmune hepatitis
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Idiopathic eosinophilic gastroenteritis
- Chronic idiopathic inflammatory bowel disease

B. Systemic

- Lupus erythematosus
- Rheumatoid arthritis
- Polyarteritis nodosa
- Granulomatosis with polyangiitis (Wegener)
- Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)

Neoplasia/clonal diseases

C. Hematological

- Lymphoma
  - Cutaneous: mycosis fungoides T-cell lymphoma (granulomatous)
  - Systemic:
  - Hodgkin
  - Non-Hodgkin
- Myelodysplastic syndrome

D. Solid tumors

- Primary: lung, breast, uterus, prostate, hepatocellular carcinoma
- Granulomatous reaction to metastases

Metabolic

E. Diabetes mellitus

F. Dyslipidemia

G. Thyroid disease

Toxic

H. Drugs: antihypertensives (angiotensin-converting enzyme inhibitors, calcium channel blockers, beta blockers, diuretics, hydralazine), hypolipidemic agents, anticonvulsants (phenytoin, topiramate), quinidine, antihistaminics, allopurinol, antimicrobials (nitrofurantoin, isoniazid), and others (beryllium, gold, copper toxicity, talc).

I. Immunotherapy and growth factors: interferon α, G-CSF, anti-TNF-α, IFN-α

Immunodeficiency

J. Common variable immunodeficiency

K. Wiskott-Aldrich syndrome

L. Chronic granulomatous diseases

Idiopathic

Table 2.
Causes of noninfectious systemic granulomas.

addressed in this chapter. Not all immune-mediated systemic processes should be assimilated as diseases capable of producing granulomas. For example, in the disease related to IgG4, although cases of pulmonary lymphomatoid granulomatosis associated with it have been described, two findings are extraordinary and practically discard it, namely, the presence of granulomas and the presence of a neutrophilic infiltrate [4, 5]. In this same sense we must refer to the diseases included in the so-called xanthogranulomatous diseases (Langerhans cell histiocytosis, Erdheim-Chester disease, Rosai-Dorfman disease, hemophagocytic lymphohistiocytosis, and juvenile xanthogranuloma) where space-occupying lesions can be seen in imaging techniques and a histiocytic infiltrate in biopsies, but rarely granulomas [6].

3.2.1 Chronic gastrointestinal and chronic biliary diseases

Granulomas have been reported in a small minority of patients with ulcerative colitis, Crohn's disease, and idiopathic eosinophilic gastroenteritis. It is unclear whether the granulomas associated with chronic idiopathic inflammatory bowel disease could be due to diseases such as primary sclerosing cholangitis or an adverse drug reaction. Granulomas may also be a feature of idiopathic eosinophilic enteritis involving the hepatobiliary tree by the disease.

Granulomas are reported very frequently (more than 50% in many series) in primary biliary cirrhosis cases. They may be portal or lobular, but are often associated with duct lesions. However, granulomas are also seen in a minority of cases in primary sclerosing cholangitis, in which they are usually well formed and non-necrotizing.

3.2.2 Vasculitis and collagen vascular diseases

Granulomas may involve the vasculature in collagen vascular diseases, like lupus erythematosus systemic, or more usually in vasculitic diseases including systemic necrotizing vasculitis and giant cell arteritis. Systemic necrotizing vasculitis is a group of heterogeneous diseases characterized clinically by a greater presentation and histologically by the presence of fibrinoid necrosis more intense than that seen in in other forms of vasculitis. Panarteritis nodosa is a vasculitis that characteristically affects the arteries of medium and small sizes. Vasculitis associated with antineutrophil cytoplasmic antibodies include granulomatosis accompanied by polyangiitis, microscopic polyarteritis, and granulomatous allergic angiitis.

3.2.3 Adverse drug reaction

After the skin, the liver is a frequent focus of granulomas secondary to drugs. Granulomas associated with adverse drug reactions may be well or poorly formed, but necrosis is very rare. Giant cells may be present, and there is a variable associated inflammatory infiltrate that may include lymphocytes, plasma cells, and eosinophils. There may be associated duct and/or vascular injury. The combination of granulomatous inflammation with significant hepatocellular injury strongly suggests drug-associated liver injury [7].

3.2.4 Primary immunodeficiency

As in severely immunosuppressed patients (transplant patients, advanced HIV, etc.), cases of primary immunodeficiencies and systemic

granulomatous complications, either primary or following opportunistic infections, may appear.

Common variable immunodeficiency comprises a heterogeneous group of diseases characterized by a significant hypogammaglobulinemia of unknown cause, failure to produce specific antibodies after immunization, and susceptibility to bacterial infections, but others develop complications, like granulomas or autoimmune diseases. Sarcoid-like granulomas are also well described in the liver, spleen, and lung in patients with common variable immunodeficiency [8]. This involvement is usually associated with other autoimmune manifestations and has a worse prognosis.

Chronic granulomatous disease is a rare primary immunodeficiency caused by an inherited defect in the genes encoding any of the NADPH oxidase components responsible for the respiratory burst of phagocytic leukocytes. The NADPH oxidase is responsible for the production of reactive oxygen species (ROS) in the activated phagocyte ("respiratory burst"). When present, mutations on the NAPDH oxidase genes do not allow ROS production, making the neutrophils of these patients incapable of destroying pathogens. These patients are especially susceptible to infections by staphylococcus, fungi and some gram-negative bacteria. The main clinical manifestations include recurrent life-threatening episodes of lymphadenitis, abscess, pneumonias, osteomyelitis, granuloma formation, and sepsis [8].

3.2.5 Interstitial granulomatous dermatitis

It is important to recognize interstitial granulomatous dermatitis, because although it can sometimes occur as an isolated skin disease, it is often associated with a systemic disease, which marks the prognosis of the patient; thus an active study should be carried out [4]. Ackerman first described this rare type of dermatitis in 1993. Although the original manifestation has been described as subcutaneous linear nodules (also known as rope sign), later reports showed a quite heterogeneous clinical spectrum ranging from hyperpigmented, erythematous papules, subcutaneous plaques, and annular lesions to firm red purplish nodules. The lesions are usually asymptomatic, but can be slightly pruritic or painful. The histopathological examination confirms the diagnosis and is characterized by a dense and diffuse interstitial infiltrate in the reticular dermis, composed of histiocytes in a palisade arrangement, sometimes with necrobiosis of collagen and neutrophils and eosinophils. Interstitial granulomatous dermatitis has been associated with various systemic diseases, including autoimmune diseases such as rheumatoid arthritis (the most common), systemic sclerosis, or lupus erythematosus. Recently, a case has been reported in association with primary biliary cholangitis. However, other etiologies have been described in isolated cases including malignancy or drugs (angiotensin-converting enzyme inhibitors, calcium channel blockers, beta blockers, diuretics, TNF-α blockers, etc.) [1, 4].

4. Diagnostic approach

The diagnostic approach must be structured, and the analytical, microbiological, or radiological tests must be adapted to the epidemiological factors of the patient's clinical history, as well as to the results of the physical examination. Obtaining a biopsy, both for histological and microbiological studies, is fundamental. In cases of uncertain etiology, close monitoring should be carried out, given the association of granulomas with potentially serious diseases (**Table 3**).

Medical history • Comorbidities (autoimmune disease, diabetes, immunosuppression) • Drugs or foreign body or water exposure • Travels • Risk exposures (sexual, parenteral drugs, etc.)
Physical examination: Clinical sign-associated diseases
Biopsy (depending on the affected organ and accessibility) • Histology • Microbiology ○ Culture (bacteria, mycobacteria) ○ PCR (mycobacteria, parasites, etc.)
Laboratory testing • Complete blood count, ESR, CRP, creatinine, calcemia, liver enzymes, LDH, glycemia, cholesterol, triglycerides, TSH/T4, serum protein electrophoresis, ANA, rheumatoid factor, angiotensin-converting enzyme • Serology for HIV, syphilis, hepatitis B and C, and others according to clinical suspicion
Mantoux or interferon gamma release assays for TB
Radiological tests • Chest X-ray and abdomen and pelvic ultrasound • Others according to clinical suspicion: CT scan, PET-CT, etc.

Table 3.
Diagnostic approach to granulomatous diseases.

5. Conclusion

- Granulomatous disorders are a heterogeneous group of diseases, including infections, systemic inflammations, neoplasia, metabolic disorders, and chemicals.

- An adequate clinical approach, together with physical examination and basic analysis, can guide the diagnostic process. However, biopsy of the lesion is usually fundamental.

- The histological type of granuloma is important in the etiological diagnosis, to optimize both treatment and follow-up.

Conflict of interest

No conflict of interests declared.

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