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Beyond the joints, the extra-articular manifestations in rheumatoid arthritis

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ABSTRACT

Rheumatoid arthritis (RA) is an inflammatory disease typically affecting the joints, but the systemic inflammatory process may involve other tissues and organs. Many extra-articular manifestations are recognized, which are related to worse long outcomes. Rheumatoid nodules are the most common extra-articular feature, found in about 30% of patients. Secondary Sjögren's syndrome and pulmonary manifestations are observed in almost 10% of patients, also in the early disease. Active RA with high disease activity has been associated with an increased risk of such features. Male gender, smoking habit, severe joint disease, worse function, high pro-inflammatory markers levels, high titer of rheumatoid factor, and HLA-related shared epitope have been reported as clinical predictors of occurrence of these rheumatoid complications. In addition, there is a little evidence deriving from randomized controlled trials in this field, thus the therapeutic strategy is mainly empiric and based on small case series and retrospective studies. However, considering that these extra-articular manifestations are usually related to the more active and severe RA, an aggressive therapeutic strategy is usually employed in view of the poor outcomes of these patients.

The extra-articular features of RA remain, despite the improvement of joint damage, a major diagnostic and therapeutic challenge, since these are associated with a poor prognosis and need to be early recognized and promptly managed.

1. Introduction

Rheumatoid arthritis (RA) is a common systemic inflammatory disease [1]; its prevalence ranges from 0.5% to 2% in general population [2]. Particularly women, smokers, and those with a family history of the disease are often affected [3]. Genetics, autoimmunity and environment factors may play a pathogenic role in the disease, although it has not fully elucidated yet [3,4]. The final result of these mechanisms is the overproduction of pro-inflammatory cytokines, such as tumor necrosis factor (TNF) and interleukin-6 (IL-6), which lead to the proliferation of synovial cells in joints and subsequent pannus formation, cartilage destruction, and bone erosions [3,5,6] Clinically, RA manifests as a chronic, symmetrical disease, initially affecting the small joints, such as proximal interphalangeal joints and metacarpophalangeal joints, and then progressing to larger ones [3,7]. Generally, these patients report pain and stiffness in multiple joints associated with an impaired quality of life [8]. Fatigue, fever, weight loss may be also present. C-reactive protein level (CPR) and erythrocyte sedimentation (ESR) are typically elevated during the active phases of the diseases [3,5,7]. Furthermore, RA is characterized by the presence of autoantibodies, typically rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA). RF is not specific of RA, since it may be present during infections and other diseases [9]. Conversely, ACPA is considered to be highly specific for the disease and it may be detected years before the onset of symptoms [10,11]. In addition, ACPA could be associated with the extent of joint destruction; synovial fluid from RA joints contains citrullinated proteins, which in turn increase the local inflammation [10]. Concerning the treatment, the methotrexate (MTX), a conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), is suggested as the first-line therapy in association with low-dosage of glucocorticoids (GCs),

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whereas leflunomide or sulfasalazine may be used as alternative options [12,13,14]. Biologic DMARDs (bDMARDs) are usually recommended when the first-line therapy does not achieve the clinical target [15]. In last years, it must be pointed out that bDMARDs have completely revolutionized the course of the disease [15], reducing the severity of structural joint damage and of joint surgery [8,16]. However, in addition to the joint involvement, RA patients may be affected by a number of extra-articular features, since it is a systemic inflammatory disease [1,3,7]. These manifestations usually identify a subset of patients with a more severe disease associated with a higher mortality and morbidity [3,17,18]. The prevalence of extra-articular manifestations is estimated to be from 17.8 to 40.9% of all RA patients [19]. Usually these features are associated with the course of RA, although they are not always associated with the severity of joint involvement and it may be dissociated from the activity of the disease [20]. In addition, it must be pointed out that the extra-articular manifestations, despite their severity, are often underweighted and undertreated, since the lack of specific guidelines. On these bases, in this work, we aimed at reviewing the extra-articular features on RA, discussing pathogenic mechanisms, clinical features, and therapeutic strategies, to provide a comprehensive review of the literature on these issues.

2. Skin involvement in RA

The skin is one of the most frequently affected extra-articular organ in RA, particularly in patients with a more severe disease (Fig. 1) [21]. Skin manifestations, usually codified as specific or non-specific, appear to be induced by different mechanisms, such as activation of the pro-inflammatory cells (neutrophils, lymphocytes, and macrophages), vasculopathy, vasculitis, acral deformity, and drugs [21].

2.1. Non-specific lesions

Non-specific lesions are more common than specific ones; diffuse skin atrophy with edema mainly on interphalangeal joints, palmar erythema and a bluish shade over the fingertips are reported in these patients [21]. Generally, in long-standing RA, the skin atrophies and becomes more fragile. Sometimes a characteristic proximal interphalangeal swelling may be associated with surrounding cutaneous atrophy which may resemble the sclerodactyly [22]. Furthermore, these patients may show some vascular changes, such as palmar erythema and a bluish discoloration over the fingertips resembling a Raynaud's phenomenon [22]. In addition, the nails are usually involved, even if it is not considered a specific RA feature. In these patients, onycholysis, longitudinal ridging (onychorrhexis), clubbing, yellow discoloration, red lunula and pterygium inversum are reported as nail involvement [22]. Splinter hemorrhages and nail fold thromboses are observed in those with RA-associated vasculitis (see below) [22].

2.2. Specific lesions

Rheumatoid nodules and neutrophilic dermatoses are considered to be specific cutaneous features of RA. Rheumatoid vasculitis, Felty Syndrome and Bywaters' lesions are other specific manifestations, although less commonly observed [21]. Some of these lesions are also characterized by peculiar histologic alterations [21].

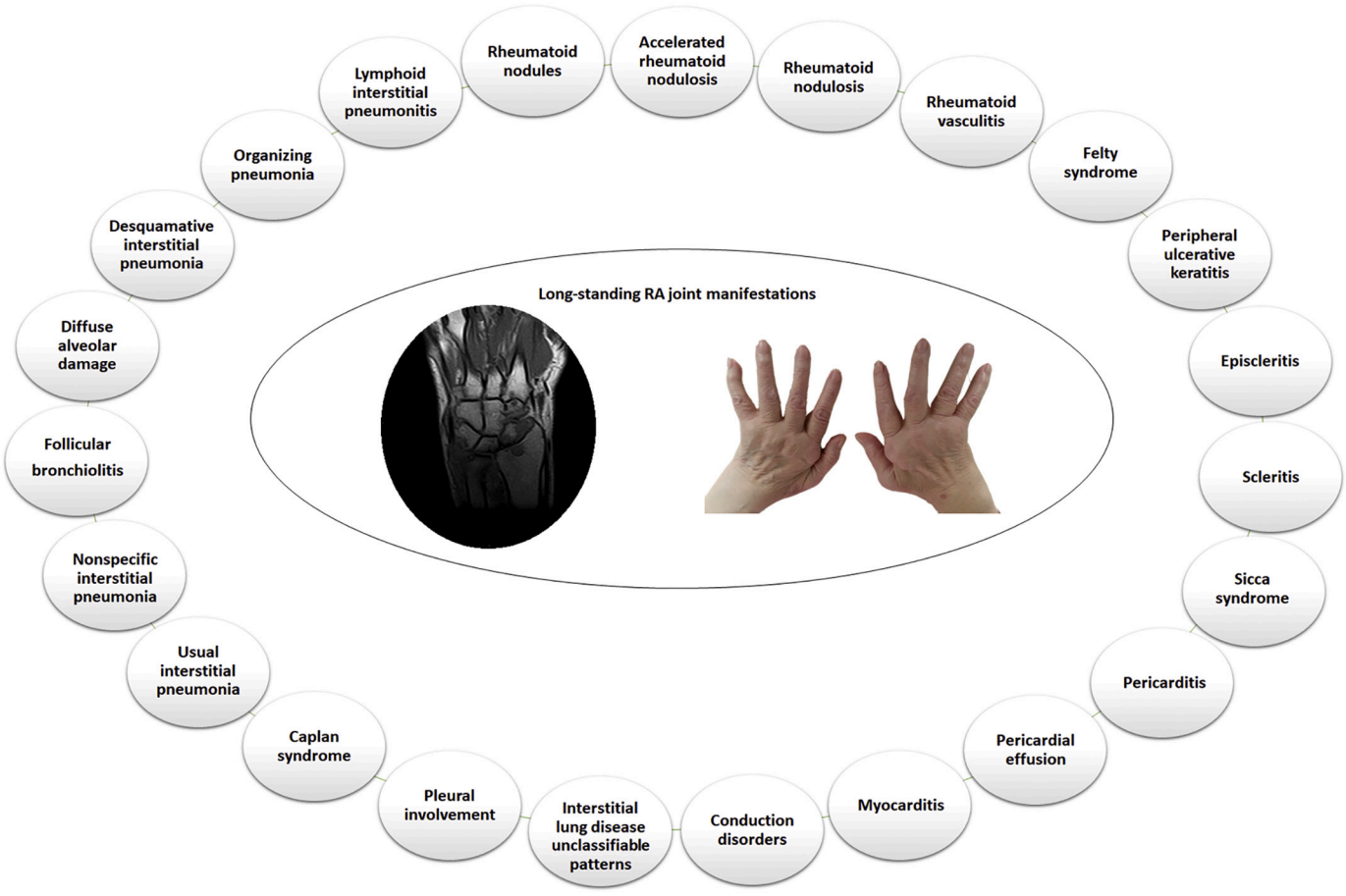

Fig. 1. Clinical manifestations of RA. Joints are typically affected in RA, but the systemic inflammatory process may involve other tissues and organs. Many extra-articular manifestations are described, as shown in the image. These are associated with a poor prognosis and need to be early recognized and managed promptly.

2.2.1. Rheumatoid nodules

2.2.1.1. Generalities and genetic associations of rheumatoid nodules. Classic rheumatoid nodules are observed in about 25% of patients and are the most common extra-articular feature of RA [23] (Table 1). These lesions are reported more frequently in the Caucasian population with a male predominance [24]. RF is reported as a predictive factor of occurrence of rheumatoid nodules, since the frequency of nodules correlates directly with its titer and less with the actual severity of the clinical picture [25]. In fact, about 90% of patients with nodular disease are characterized by the presence of such autoantibody [22]. Furthermore, 40% of seropositive patients show rheumatoid nodules, whereas only 6% of seronegative patients display these features [26]. It has been reported that the appearance of rheumatoid nodules is associated with a specific genetic background [27]. The HLA-DR4 haplotype (including the heterogenous group of DRB1 alleles) is a predictive factor of subcutaneous nodules [27]. RA patients with heterozygosity for HLADRB1 alleles, specifically *0401 with B1*0404/8 or *0101, are at higher risk for nodular disease and even more severe RA prognosis [27]. Homozygosity for HLA-DRB1*0401 is associated with a susceptibility to major organ involvement such as rheumatoid lung disease, rheumatoid vasculitis, Felty's syndrome, and rheumatoid vasculitic mononeuritis [28].

2.2.1.2. Pathogenic mechanisms of rheumatoid nodules.. The pathogenesis of rheumatoid nodules is not entirely clarified yet, and a number of different theories have been proposed [29,30,31,32]. RF involvement is reported to be the cause of locally immune complex aggregation and of local macrophages stimulation [22]. In fact, Kato et al. showed that the aggregation of IgM-RF on the endothelial cell surface, following a vascular injury, could result in immune complexes formation contributing to the development of rheumatoid nodules [31]. In addition, a growing neoangiogenesis and granulation tissues are observed in the early nodules suggesting the role of minor and repeated trauma as inciting events [22]. These pathogenic events result in the release of fibrin as procoagulant response to the angioneogenesis [21]. In addition, secreted macrophage chemotactic factors and the interaction of macrophage receptors with fibrinoid and fibronectin, which are deposited at the margins of the nodule's inner core of necrosis, may attract a centrifugally expanding array of macrophages [24].

2.2.1.3. Clinical features of rheumatoid nodules. Nodules are skin colored, may be solitary or multiple, and range from 5 mm to many centimeters in diameter. Usually, nodules lie deeply subcutaneously, but there also are some epidermal and freely movable ones [26]. Some rheumatoid nodules are firm and painless, but other, those found on the plantar surfaces, may be associated with some discomfort. Clinically, rheumatoid nodules are commonly found at the site of recurrent mechanical pressures or repeated trauma, such as extensor surfaces of olecranon, forearm, fingers, occipitus, back, sacral prominences and heels. These are unusually reported on sites like feet, buccal mucosa, vulva and penis [22]. Rheumatoid nodules may be also observed on many extracutaneous organs, including lungs, pleura, pericardium, heart, pharynx, vocal cords, peritoneum, dura, sclera, and liver. In these organs, the presence of such nodules should be carefully assessed since the possibility of mimicking neoplastic lesions [33]. Additional differential diagnosis of rheumatoid nodules includes tumoral calcinosis, fibromas, xanthomas, subcutaneous sarcoidosis, metastatic tumors, histoplasmosis, amyloidosis, ganglion cysts, foreign body granuloma, basal cell carcinoma, epidermoid cysts, and synovial cysts [34].

Usually, the diagnosis of rheumatoid nodules is based on clinical findings, whereas histology is required when these lesions are located on unusual sites or without other signs of RA [22]. The analysis of rheumatoid nodules composition shows granulomas in different stages of development separated by a scar tissue, which contains a haphazard distribution of small vascular islands composed of lymphocytes, plasma cells, and histiocytes [22]. Generally, the nodule grows and matures into 3 definite histologic zones: i. the first is an inner central necrotic zone that is amorphous and eosinophilic and includes collagen fibrils, fibrin, proteins, and other cellular debris; ii. the second, composed of palisading macrophages that express HLA-DR antigen, surrounds the first, and these macrophages migrate toward the central zone and have high turnover; iii. The third one is an outer layer of perivascular granulation tissue which consists of infiltrative chronic pro-inflammatory cells [22].

2.2.1.4. Therapy of rheumatoid nodules. In general, nodules are asymptomatic, therefore a specific therapy is not required. These nodules should not be drained, injected, or excised, because of the high risk of infection or recurrence with such interventions [35]. The surgical removal may be considered if nodules are debilitating, ulcerated, infected, compressing a nerve, or causing a limited range of joint motion [22]. However, it must be pointed out the local granulation tissues may often complicate these areas post-operatively. Rheumatoid nodules usually decrease when RA disease activity is effectively controlled [36].

2.2.2. Rheumatoid nodulosis

Bywaters in 1949 described the rheumatoid nodulosis as a variant of RA characterized by subcutaneous nodules and associated cystic bone lesions, in the setting of a palindromic rheumatism [37]. In about 80% of patients, rheumatoid nodulosis is observed in male gender aged between 30 and 50 years [37]. Different patterns of rheumatoid nodulosis have been suggested by Couret: i. multiple subcutaneous rheumatoid nodule identified by biopsy; ii. recurrent joint symptoms with minimal clinical or radiologic involvement; iii. Benign clinical course; iv. no or mild systemic manifestations of RA [37]. RF seropositivity and radiologic evidence of subchondral cystic involvement of small bones are frequently observed, although their absence could not fully exclude the rheumatoid nodulosis as a diagnostic possibility [38].

Rheumatoid nodulosis is self-limited and symptomatically controlled with nonsteroidal anti-inflammatory drug (NSAIDs) [38]. Complete resolutions with hydroxychloroquine have been also described [39].

2.2.3. Accelerated rheumatoid nodulosis.

In 1986 Kremer and Lee defined the accelerated rheumatoid nodulosis as a complication of MTX administration in patients with RA [40]. It is characterized by rapid onset and worsening of nodules in chronic RA patients during MTX therapy; 8–11% of MTX-treated RA patients, after a variable duration from the beginning of the therapy [20,22]. This kind of rheumatoid nodulosis is more frequent in male patients and may occur without the presence of pre-treatment rheumatoid nodules [22]. The difference with the classical rheumatoid nodule is that the lesions are smaller and distributed in different sites, such as the metacarpophalangeal and proximal interphalangeal joints of the hands and

Table 1
Rheumatoid nodulosis.

RA nodulosis	Clinical features	Treatment
Rheumatoid nodules	- Skin colored - From 5 mm to many cm in diameter - Generally firm and painless - Found at the site of recurrent mechanical pressure or trauma	- Specific therapy in not required - Surgical removal if nodules are debilitating or causing a limited range of joint motion
Rheumatoid nodulosis	- Subcutaneous nodules and associated cystic bone lesions in the setting of a palindromic rheumatism	- Self-limited and symptomatically treated with NSAIDs
Accelerated rheumatoid nodulosis	- Onset during MTX therapy - Smaller than rheumatoid nodules and distributed in different sites	- Regression with discontinuation of MTX therapy

feet, and on the ears [41]. The pathogenetic mechanisms of accelerated rheumatoid nodulosis are still unclear. Increased frequency of HLA-DRB1*0401 and RF seropositivity have been associated with accelerated rheumatoid nodulosis, although seronegativity could not exclude this diagnosis [36]. Histopathologically, accelerated rheumatoid nodulosis may be identical to non-MTX-induced rheumatoid nodules. [36].

Accelerated rheumatoid nodulosis often regresses with discontinuation of MTX therapy and reappears once MTX is restarted. Hydroxychloroquine, colchicine, and sulfasalazine have been shown to decrease nodules frequency in MTX-induced accelerated rheumatoid nodulosis [22].

2.2.4. Felty syndrome

Felty syndrome, first described by Felty et al. in 1924, is defined by the classic triad of arthritis, leukopenia, and splenomegaly [21]. About 1% of RA patients may show the Felty's triad [42,43,44]. It generally affects in patients with a long history of RA, seropositive, and destructive arthritis [22,42] Skin manifestations of Felty syndrome include the presence of rheumatoid nodules (76% of patients), hyperpigmentation, and leg ulcers (22% of patients) [22]. Although different factors have been suggested, the most frequent pathogenic mechanism is the venous insufficiency complicated by the vasculitis [45]. Ulcers are chronic and deep, are located over the shins and ankles, and are usually followed by red blood cell extravasation, resulting in a typical hyperpigmentation [22]. It has been reported that Felty patients have an increased risk of melanoma during the first year of diagnosis. They also have an increased risk of lymphomas and leukemias [46]. This association seems to be related to the presence of the neutropenia, splenic dysfunction, aggressive rheumatoid disease, and increased susceptibility to Epstein-Barr viral infection [46]. In addition, neutropenia is also the cause of an increased risk of infection in these subjects [47]. Poor prognosis has been associated to Felty syndrome with a mortality rate of up to 25%, with deaths often due to sepsis [21]. Differential diagnosis includes systemic lupus erythematosus (SLE), drug-induced leukopenia, viral infection, amyloidosis, leukemia, lymphoma, subacute bacterial endocarditis, aplastic anemia, splenic abscess, hemolytic anemia, tuberculosis, and Sjogren's syndrome [47].

The therapeutic strategy of Felty syndrome comprises sulfasalazine, hydroxychloroquine and MTX; in non-responder patients, rituximab may be a therapeutic option [48]. Neutropenia ad recurrent infections should be also considered, eventually recombinant granulopoietic growth factors could be administered [48].

2.2.5. Rheumatoid vasculitis

Rheumatoid vasculitis is an inflammatory involvement of blood vessels, leading to a variety of clinically relevant skin and systemic issues [22] (Table 2). Independently of joint involvement, rheumatoid vasculitis has been observed in almost 25% of patients in postmortem biopsies and in up to 30% of biopsies of clinically uninvolved sites [49,50,51]. Generally, it occurs in a long-standing disease (10 to 14 years after arthritic onset) and it is associated with rheumatoid nodules [52]. The annual incidence of rheumatoid vasculitis is 1% [53]. Male patients with multiple rheumatoid nodules, joint erosions, high titer of RF are considered at higher risk to develop rheumatoid vasculitis [54].

2.2.6. Pathogenesis

Rheumatoid vasculitis is codified as a type III hypersensitivity reaction, in which immune complexes may activate the complement cascade, triggering the chemotactic recruitment of neutrophils and causing endothelial damage [55].

High C-reactive protein levels and signs of complement consumption have been implicated in circulating immune complexes (CICs) deposition in this condition [22].

Flipo et al. proposed a TH1-mediated process leading to an observed increase in ICAM-1, *E*-selectin, and expression of tumor necrosis factor-a in endothelial cells and perivascular infiltrative cells in active rheumatoid vasculitis lesions [56].

Table 2
Skin lesions in rheumatoid vasculitis.

Cutaneous ulcers	Open skin sore caused by an obstruction of the small blood vessels in the superficial ulcers or obstruction of medium vessels in a deeper ulcer.
Localized petechiae	Pinpoint non-blanching spots that measure less than 2 mm in size.
Palpable purpura	Non-blanching spot that measures greater than 2 mm resulting from the leakage of blood into the skin through inflamed, damaged blood vessels.
Hemorrhagic blisters	Thin blood-filled vesicles.
Digital infarcts (including nail fold or edge involvement)	Small spots around fingernail.
Gangrene	Death of body tissue resulting from a profound lack of blood flow.
Non-specific maculopapular erythema	Redness of the skin caused by congestion of the capillaries in the lower layers of the skin
Livedo reticularis	A mottled purplish discoloration of the skin.
Erythema elevatum diutinum	Red, purple, brown or yellow bumps of different sizes that grow on or just below the skin.
Atrophie blanche	Small smooth white areas on the skin with hyperpigmented borders and teleangectasis, developing into atrophic stellate scars.

2.2.7. Clinical features

Rheumatoid vasculitis is characterized by heterogeneous clinical and histological features; it may virtually involve any organ, more frequently skin and peripheral nervous system [57].

The skin involvement may manifest in different ways, as reported in Table 2 [22]. Nail fold infarctions, the so-called Bywaters lesions, are a characteristic clinical feature of rheumatoid vasculitis [58], related to the occlusive arteritis and intimal proliferation in small vessels [58]. These are small (0,5–1 mm), purpuric, painless and transient papules, which appear on the distal fingers, generally on nail-fold, nail-edge, or digital pulp [59]. Although frequently unnoticed, the digital lesions are the most recurrent finding of rheumatoid vasculitis [52]. Typically, Bywaters lesions are not associated with systemic vasculitis [60] and have a favorable prognosis [58].

In about 10% of RA patients [61], rheumatoid vasculitis may induce acute and painful leg ulcers (generally located on the lateral malleolus or pretibial region) [62]. The cause is multifactorial, mainly attributed to vasculitis and venous insufficiency [63].

Patients may also experience urticarial vasculitis, characterized by wheals persisting for more than 24 h and healing with hyperpigmentation [54].

About 50% of patients may show evidence of peripheral nerve lesions as multiplex mononeuritis or sensory symmetric neuropathy, as a manifestation of peri- or epineural arteritis [64].

Systemic involvement is quite rare (less than 1% of patients with rheumatoid vasculitis) and it could be found hepatomegaly, splenomegaly, pericarditis, arrhythmia, alveolitis, scleritis, proteinuria, hematuria, mononeuritis multiplex, polyneuropathy, bowel ulcers, cerebral infarction, and acute abdomen [49].

2.2.8. Diagnosis

There are no standard diagnostic criteria for rheumatoid vasculitis. Diagnosis may usually be made based on a medical history, laboratory tests, and histopathological examination of the areas involved [57]. Biopsy is necessary for a correct diagnosis in case of clinical suspicion of rheumatoid vasculitis. Histologically, dermal small capillaries, post-capillary venules, and medium sized arteries may be simultaneously involved [55]. In the same sample, different types of vasculitis may be observed at the same time [55]. Generally, rheumatoid vasculitis of small vessels is a leukocytoclastic vasculitis characterized by neutrophilic and eosinophilic infiltrates with leukocytoclasia, red blood extravasation, and fibrinoid necrosis of blood vessel walls [55].

Rheumatoid vasculitis of medium-sized vessels, located at the dermal-subcutaneous junction, may be histologically indistinguishable from polyarteritis nodosa, characterized by segmental and concentric necrotizing vasculitis of medium-sized arteries with neutrophilic debris, fibrin, and red blood cells extravasation [55].

Patients with rheumatoid vasculitis often have RF (the most typical laboratory feature), hypocomplementemia, high levels of CICs, and possible high sera levels of cryoglobulin [65,66]. Other findings include anemia, leukopenia, leucocytosis, eosinophilia, thrombocytosis, elevated ESR, and abnormal nerve conduction velocities [55].

In diagnosing the systemic rheumatoid vasculitis, the presence of one or more of the following criteria have been suggested: i. multiplex mononeuritis or peripheral neuropathy, ii. peripheral gangrene, iii biopsy evidence of acute necrotizing vasculitis plus systemic features of the disease (e.g. fever, weight loss), iv. deep cutaneous ulcers or active extra-articular disease (e.g. pleurisy, pericarditis, scleritis) if associated with typical digital infarcts or biopsy evidence of vasculitis [67]. Other causes of such lesions should be excluded, such as atherosclerosis or diabetes mellitus [67].

Rheumatoid vasculitis may be confused with a variety of other conditions (polyarteritis nodosa, leg ulcers can resemble pyoderma gangrenosum) [22]. Differential diagnosis of vasculitis with arthritis includes systemic lupus erythematosus, Wegener granulomatosis, and erythema elevatum diutinum [22].

2.2.9. Prognosis and therapy

Significant morbidity and mortality may occur in patients with rheumatoid vasculitis, up to 43% [68], especially within the first 6 months from the onset of vasculitis [52]. Higher RF levels are associated with higher mortality [69]. Prognosis depends on the size of blood vessels involved and the severity of systemic manifestations [54]. Cutaneous rheumatoid vasculitis without systemic complications has a relatively benign prognosis [69]. Nail-fold infarcts need no specific therapy [49]. Digital infarction, multiplex mononeuritis, fever, and other systemic manifestations require a prompt aggressive therapy [49]. Usually, GCs and cyclophosphamide have been used to treat rheumatoid vasculitis [57]. Anti-TNF inhibitors and rituximab have been also considered as possible therapeutic options [68,69].

3. Rheumatoid ocular involvement

RA is the most common rheumatic disease (prevalence 0.8–1%) which leads to an ocular involvement. In fact, approximately 25–39% of patients experience such complication and, sometimes, it may be the first sign of the disease [70] (Fig. 1). The probability of ocular involvement increases with the duration of the disease and it may represent the main clinical manifestation in patients with a long-standing disease [70,71]. In addition, there is an association between the presence of ACPA and the ocular manifestations [71]. Considering that the eye is considered a privileged immune site, since its microenvironment is composed by immunosuppressive factors (this status may preserve the tolerance from external triggers), the ocular involvement in RA could identify a more severe pattern of the disease [72].

Usually, among the ocular manifestations of RA, scleritis, episcleritis, keratitis, and dry keratoconjunctivitis (KCS), are reported [70] (Table 3). Generally, the form of the KCS is independent of RA disease activity [70]. Episcleritis (0.17–3% of patients) or scleritis (0.67–6% of patients) [70], both diffuse and necrotizing, are less common [70,73]. Overall, RA is responsible for about 10–20% of all scleritis. Peripheral ulcerative keratitis (PUK) is the rarest ocular manifestation of RA (0.1–2% of patients) [73]. KCS (15–28% of patients) is the most frequent, due to inflammatory infiltration of the lacrimal gland [70].

3.1. Scleritis and episcleritis

Scleritis and episcleritis burden the clinical course of RA [73]. The Watson classification system classifies scleritis into three main types: i. episcleritis, ii. anterior scleritis, iii. Posterior scleritis [74]. Episcleritis is associated with a pro-inflammatory process of the superficial layer of the sclera. The anterior scleritis is related to a pro-inflammatory involvement of deeper layers of the anterior portion of the sclera, whereas during the posterior one, the inflammation involves the area behind the insertion of the rectus muscle [74].

Table 3
Ocular involvement in RA.

The ocular involvement in rheumatoid arthritis	Clinical features	Treatment
Scleritis	- Chronic eye pain radiating to the face and scalp, like temporal arteritis, worsening during the night - Red eye - Reduced visual acuity	- NSAIDs - Vision-threatening complications require intravenous boluses of methylprednisolone - For refractory or poor responsive clinical pictures, cyclophosphamide, cyclosporine or bDMARDs (infliximab or rituximab)
Episcleritis	- Tenderness or mild pain over the affected area - Not associated with visual loss or photophobia	- Resolve without intervention - Topical glucocorticoids
Peripheral ulcerative keratitis	- Red eye - Pain over the affected area	- NSAIDs - Glucocorticoids - For refractory clinical pictures, bDMARDs (infliximab or rituximab)
Keratoconjunctivitis sicca	- Ocular burning - Painful superficial keratitis - Itching - Sensation like having sand in the eyes	- Artificial tears - Pilocarpine, may be used to stimulate lachrymal secretion

3.1.1. Episcleritis

The prevalence of episcleritis in RA is 0.17% and the pathogenesis is still unknown [75]. Episcleritis manifests as diffuse redness of one eye in 80% of episodes, even if a bilateral involvement is reported [75]. This RA complication is not associated with neither visual loss or photophobia, patients often describe tenderness or mild pain over the affected area [76,77]. An uncommon and peculiar form is the nodular episcleritis, which is a nodule of inflamed tissue characterized by edema and infiltration of the episcleral tissues [75,77]. Most episodes of episcleritis resolve without intervention; once required, the treatment of symptomatic episcleritis is topical GCs, such as fluorometholone or loteprednol etabonate. Such therapy may be administered four times a day for 1 to 2 weeks until the resolution of the clinical picture [75]. In case of lack of response, NSAIDs, including, ibuprofen or naproxen, may be administered [77,78]. Generally, none of the patients required systemic GCs therapy or other immunosuppressive drugs.

3.1.2. Scleritis, clinical features

The prevalence of scleritis in RA is about 0.2–6.3%, and usually the diagnosis of RA precedes the onset of scleritis [73]. Currently, the exact pathophysiology of scleritis is not well defined [79]. During scleritis, the biopsy of affected tissues may show an infiltrate of pro-inflammatory cells like macrophages and T cells, which could play a pathogenic role by producing mediators of inflammation [79]. Vascular occlusion, fibrinoid necrosis and vascular infiltration are the main observed features [79]. The scleral inflammation associated with RA may be codified as follows: i. diffuse or nodular, ii. anterior or posterior, iii. necrotising or non-necrotising [73,74]. Basically, it is an inflammation of the sclera, clinically manifesting as a chronic eye pain radiating to the face and

scalp, like temporal arteritis, worsening during the night. It is also associated with red eye and reduced visual acuity [75,77]. The painful lesions of the sclera may also involve the cornea and even the underlying uvea [77,80].

3.1.3. Therapeutic strategy of scleritis

The anterior scleritis may be treated by NSAIDs [81], whereas the management of necrotising disease requires systemic GCs with a recommended starting dose of 1 mg/kg per day [81]. Vision-threatening complications require intravenous high dosages of GCs [81]. For refractory or poor responsive clinical pictures, cyclophosphamide, cyclosporine or bDMARDs, such as an anti-TNF agent or rituximab, may be considered [82,83,83,84,85,86]. In addition, synthetic DMARDs, including MTX, mycophenolate mofetil, and azathioprine may be used as steroid-sparing agents [77,87]. Despite the severity of clinical picture and possible *sequalae,* there are currently few randomized controlled trials for the treatment of scleritis [88,89,90]. A phase I/II non-randomized, prospective, single-center study evaluated the efficacy of subcutaneous gevokizumab, an anti-interleukin 1β (IL-1β) monoclonal antibody, in 8 RA patients with active, non-infectious, non-necrotizing anterior scleritis. In this study, a large majority of patients reported an improvement of ocular involvement without significant adverse events [89]. In another study, a prospective, dose-ranging, randomized, double-masked phase I/II clinical trial, 12 patients with non-infectious refractory scleritis, from either RA or other rheumatic diseases, were randomized to receive 500 or 1000 mg of rituximab twice after 15 days. After 24 weeks of therapy, 9 patients showed an improvement of scleral inflammation [90].

3.2. Peripheral ulcerative keratitis

PUK is a type of inflammatory damage that occurs in the limbal region of the cornea [73]. It is combined with an epithelial defect and the destruction of the peripheral corneal stroma [73,91]. The presence of PUK has been proposed as a marker of severity in RA, since it is associated with a more aggressive subset of the disease [91,92]. Although the pathogenesis of PUK has not been fully elucidated in RA, some studies suggested that T-cell and B-cell hyper-activity could promote the formation of immune complexes, which could be deposited on the marginal cornea [93]. Consequently, the complement pathway could be activated, inducing the recruitment of pro-inflammatory cells to the cornea, such as neutrophils and other proteases secreting cells [94].

Usually, PUK manifests with red eye and pain, excess discharge, and blurred or decreased vision. The most important complication of PUK is the onset of a corneal fusion process [94]. Systemic GCs or NSAIDs are usually required, particularly during the acute phases [77]. Immunosuppressive drugs may be used in later stages; infliximab and rituximab have been used in refractory clinical pictures [95,96]. In addition, corneal transplantation may be performed in the most severe cases [73,77].

3.3. Keratoconjunctivitis sicca

KCS is the most frequent ocular complication of RA [97]. Usually, RA patients are affected by a secondary Sjögren's syndrome [75,97,98]. The immunopathogenesis of dry eye disease is still unknown in RA [99]. It has been proposed that repeated stresses to the ocular surface could activate mitogen-activated protein kinase's (MAPK) pathways, such as p38 and c-Jun N-terminal kinases (JNK), and nuclear factor (NF)-κB, which, in turn, could stimulate the production of pro-inflammatory mediators by the ocular surface epithelium, including IL-1β, TNF, and IL-8 [99]. Consequently, pro-inflammatory cytokines, chemokines, and matrix metalloproteinases lead to the expansion of autoreactive T helper cells which infiltrate the ocular surface and lacrimal glands [99]. KCS is a chronic condition characterized by a decrease in lachrymal film secretion by the principal and accessory lachrymal gland, possibly evolving toward severe damages [77,100]. Two main KCS forms may be codified, which are not mutually exclusive, based on the glands involved: i. hyposecretion, if the principal lachrymal glands are involved, ii. hyper-evaporation, if there is a damage of the accessory lachrymal gland [100]. The main clinical features of this condition are sensations of ocular burning, painful superficial keratitis, itching, visual deficiencies, redness and a sensation like having sand in the eyes. Schirmer's test generally indicate a hyposecretion [101]. This ocular involvement in RA may lead to a lachrymal instability with qualitative changes in the lachrymal film, as showed by break-up time, the number of seconds that elapse between the last blink and the appearance of the first dry spot in the tear film [102]. Artificial tears are the first-line therapy for dry-eye syndrome [102]. Moreover, systemic therapies, such as pilocarpine, may be used to stimulate lachrymal or salivary secretion [102]. Weifang et al. investigated the relationship between dry eye and the disease activity in patients with RA [103]. Thirty RA patients were enrolled, who had carried out medical treatment in the hospital and screening for cataract whereas other patients were enrolled by internet [103]. All RA patients were investigated by the ocular surface disease index (OSDI) questionnaire, measurement of tear film break time (TBUT), measurement of tear meniscus height (TMH), measurement of Meibomian gland secretion score (MSS), measurement of eyelid margin assessment (EMS), corneal fluorescein staining (CFS) [103]. Furthermore, these patients were compared with 20 healthy controls [103]. TBUT was lower for the RA group than healthy controls. The scores of MS, CFS, MSS and EMS were significantly higher in the RA whereas there were no significant differences between both groups for OSDI and TMH [103]. However, 18 out of 30 RA patients had active disease and they showed significant differences for CFS scoring compared to other 12 RA patients with no active disease. No significant differences were retrieved about dry eye were observed between patients with active and no active disease [103].

4. The heart involvement in RA

The heart involvement is another extra-articular manifestation of RA associated with the mortality of these patients, since it is associated with the occurrence of heart failure [104,105]. All layers of the heart may be involved in RA patients [104,106]. Pericarditis is the most common form of cardiac involvement in RA patients [107]. Moreover, pericardial effusion, myocarditis and conduction disorders may be recognized in RA although less frequent [104,105,107]. We have not reviewed cardiovascular disease because of multiple lines of evidence are largely present in available literature [108,109,110]. In fact, it is well-know that the rheumatoid inflammatory process and the traditional cardiovascular risk factors could synergize in enhancing the cardiovascular burden of RA patients [106,111,112].

4.1. Pericarditis

Pericarditis is another cardiac manifestation of RA [104]. The prevalence of pericarditis is clinically estimated in almost 10% of patients, whereas considering echocardiographic and/or post-mortem, it ranges about 30–50% [104,107,113] Pericarditis occurring in RA displays non-specific histological characteristics, except for rheumatoid nodules, which have been reported in post mortem studies [104,113]. The exact pathogenic mechanisms of rheumatoid pericarditis are still unknown [104]. It occurs with a sharp pleuritic chest pain, pericardial friction rubs and, in severe cases, pericardial tamponade [114]. Pericarditis is treated empirically with NSAIDs, particularly aspirin, which usually takes two weeks [115]. Although there are no randomized controlled trials in RA patients, colchicine may be used to improve the clinical response in recurrent pericarditis or pericarditis that does not respond to conventional therapy [116]. Furthermore, ESC guidelines suggest colchicine as first-line therapy in addition to NSAIDs, because of dual therapy may decrease the symptoms and rate of recurrence

[116,117]. In addition, in RA patients, GCs may be considered as a further therapeutic option to treat the pericarditis [116].

In addition, RA patients have a greater risk of developing pericardial effusion than healthy controls [107]. There are two proposed mechanisms of accumulation of pericardial fluid. The first one is the development of exudate associated with the pro-inflammatory process [116]. The other one is the decreased reabsorption, due to a general increase in systemic venous pressure, which may lead to the development of a transudate. The main symptoms, when present, of pericardial effusions are dyspnea on exertion progressing to orthopnea, chest pain and/or fullness [116]. The compression of local structures may also generate nausea, dysphagia, hoarseness, hiccups. The management of pericardial effusion is the same of pericarditis [115]. Drainage of the effusion should be considered in symptomatic pericardial effusion without evidence of inflammation or when empiric anti-inflammatory drugs are not successful [116].

4.2. Other cardiac manifestations

Myocarditis is also a complication of RA, although clinically uncommon [116]. Usually, it is a subclinical feature without known cardiac disease. In fact, cardiac MRI studies have shown that subclinical myocardial abnormalities may be frequently observed in RA patients [118,119]. The exact pathogenesis is still unknown [118]. Myocarditis is usually histologically defined by the presence of an inflammatory infiltrate in the myocardium with a damage of cardiomyocytes [119]. Clinically, patients may experience chest pain, palpitations, syncope, and dyspnea. Cardiogenic shock is a possible complication of this situation [119]. GCs are the first-line therapy and immunosuppressive therapies such as azathioprine and cyclophosphamide may be used if GCs are not enough to control the disease [116]. In this context, it is presently ongoing a clinical trial effects of abatacept on myocarditis in RA (AMiRA) to evaluate the effects of abatacept in subclinical myocarditis in RA diagnosed by cardiac FDG PET/CT imaging [120].

RA patients may have signs related to a cardiovascular autonomic dysfunction (CAD) [121]. The prevalence rate of CAD is about 0–25%, usually identified by a prolonged QT interval on ECG [121]. The latter could also be a useful indicator of excess risk for cardiovascular mortality, because of ventricular arrhythmias which are associated with QT prolongation [122]. Concerning possible therapies, 13 RA patients with QT prolongation received Tocilizumab (TCZ), once every 4 weeks and they showed a significant reduction of the QTc interval to mean values < 440 msec associated with a reduction of CRP levels [122]. Despite the small sample size and the short duration of the follow up period, these findings could suggest the possible usefulness of immunomodulatory therapies in managing these cardiac conduction disorders in RA [122].

5. Pulmonary involvement in RA

5.1. Generalities of rheumatoid lung disease

Pulmonary involvement represents a common extraarticular manifestation of RA and it remains one of the main causes of morbidity and premature mortality during the disease [123,124,125]. In fact, after cardiovascular complications and comorbidities, the pulmonary disease has been recognized as an important cause of death on these patients [126]. The prevalence of the pulmonary disease ranges between 5% and 30%, reaching even 67% in some studies [127,128]. Any lung compartment may be interested, including pleura, the large and small airways, lung interstitium, and pulmonary vessels [129]. Occasionally, the pulmonary symptoms may precede the articular ones [130]. Clinically, lung involvement may present as different patterns of interstitial lung disease (ILD), pleural disease, rheumatoid nodules, upper airway disease (such as cricoarytenoiditis) or lower airway disease (such as follicular bronchiolitis) (Table 4) [131,132,133,134].

Table 4
Lung involvement in RA, CT and histological features.

Pattern	CT features	Histological features
UIP	- Honeycombing - Reticulations - Traction bronchiectasis - Clustered cystic airspaces	- Fibroblastic foci - Hyalinized collagen - Smooth muscle and elastofibrosis
NSIP	- Ground-glass opacities - Reticular Opacity - Traction bronchiectasis	- Lymphocytic infiltration - Plasmacytic infiltration - Uniform accumulation of collagen
OP	- Focal sub-pleural consolidation - Peribronchovascular airspace consolidation - Ground glass opacities - Air bronchogram sign	- Fibroblastic plugs in alveolar sacs and ducts - Granulation tissue buds (Masson bodies)
LIP	- Ground glass opacities - Centrilobular nodules - Lymph node enlargement - Bronchovascular thickening	- Lymphocytic infiltration - Plasmacytic infiltration - Histiocytes - Germinal centers
DAD	- Ground glass opacities - Reticulation - Traction bronchiectasis - Consolidation area	- Eosinophilic strands of necrotic cells - Protein - Fibrin - Hyperplasia of type II pneumocyte
DIP	- Ground glass opacities. - Microcystic changes - Reticular lines.	- Macrophage accumulation in alveolar spaces. - Lymphocytic conglomerates
FB	- Centrilobular nodule - Ground glass opacities - Tree-in-bud opacities	- Hyperplastic lymphoid follicles - Germinal centers

5.2. Interstitial lung disease

ILD is a common feature in RA (Fig. 2), its estimated prevalence increases according to the disease duration. In early disease, ILD-related HRCT features were identified in about 25% of patients at the onset of the disease and almost 30% developed it within 2 years [135,136,137]. Furthermore, in longstanding disease, a prevalence of HRCT-ILD in some studies is estimated in almost 70% [128].

5.2.1. Pathogenesis

The etiology of RA-ILD is not completely understood, although genetic, humoral and environmental factors seem to be involved [138,139,140,141]. The rheumatoid inflammatory process, mediated by cytokines, chemokines, and growth factors, may promote fibroblasts proliferation and differentiation toward myofibroblasts, thus increasing synthesis and deposition of extracellular matrix. In addition, this pathogenic scenario is furtherly complicated by the possible ILD-promoting effects of some drugs used to treat RA, such as cs- and bDMARDs, as well as different environmental agents (e.g. smoking habit, irritants and adjuvants) [142,143,144,145,146,147]. Smoking habit is the most relevant exogenous risk factor not only for ILD development but also on RA occurrence [148,149]. In fact, many studies support a direct pathogenic link between smoking habit and seropositive RA, since an important role of smoke has been suggested in auto-antibodies production [149,150,151,152,153,154].

Interestingly, some Authors suggest that the immune tolerance breakdown could take place in the lung with possibly a subsequent spreading of an immune response to joints. In fact, there is a subset of RA patients who are ACPA positive with isolated lung and not articular involvement [155,156]. The potential explanation of this feature is related to the lung injury from cigarette smoking which may contribute to citrullination of some lung proteins, finally leading to the development of specific and typical RA auto-antibodies [157]. In fact, the mechanism of citrullination, the post-translational enzymatic conversion of arginine to citrulline operated by increased activity of peptidylarginine deiminases (PAD) enzymes, may be induced by the smoking [158].

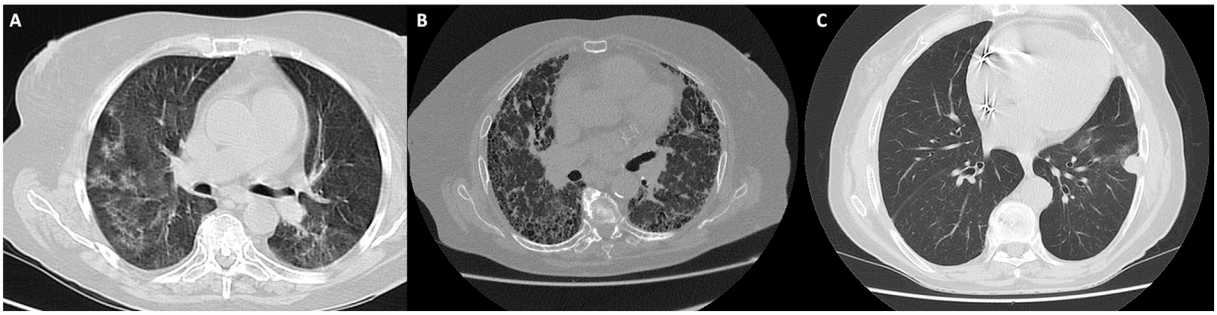

Fig. 2. Representative images of HRCT in RA. Different patterns of HRCT lung involvement are recognized in RA patients; A) ground glass opacities, B) interstitial inflammation and honeycombing affecting subpleural areas, C) rheumatoid nodule are shown, respectively.

In patients with the shared epitope HLA-DRB1, citrullinated residues may act as neoepitopes that break immunologic tolerance and become a target for autoimmunity. It has been hypothesized that citrullination could increase the binding of peptides to HLA-DRB1 shared epitopes, therefore increasing the immunogenicity of these proteins [159,160,161,162,163,164]. A large Sweden case-control study demonstrated a 21-fold increased risk of developing RA among patients who were ACPA, smoked and had two copies of the shared epitope gene versus non-smokers without the shared epitope gene [157]. Similarly, Restrepo et al. showed a strong association among HLA-DRB1 shared epitope, cigarette smoking, and the development of RA-ILD. They also reported an association between high titer of ACPA and RA-ILD [165,166]. Other genetic factors, associated with increased risk of ILD in RA, were represented by HLA-B54, HLA-DQ1B*0601, HLA-B40, HLA-DR4, and the site encoding α-1 protease inhibitor [167].

5.2.2. *Different patterns of RA-ILD*

The description of RA-ILD follows the American Thoracic Society/ European Respiratory society international consensus classification of idiopathic interstitial pneumonias [168,169].

Usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP) are the most common histopathologic patterns in RA, ranging about 40–60% and 11–30% of patient, respectively [170]. Other possible patterns are organizing pneumonia (OP, 8%), lymphoid interstitial pneumonitis (LIP, <2%), desquamative interstitial pneumonia (DIP, <1%), diffuse alveolar damage (DAD, <2%) and follicular bronchiolitis (FB, 8%). mixed or unclassifiable patterns are also present.

UIP is characterized by a heterogeneous pattern in which areas of normal lung are interspersed with areas of active fibrosis (known as fibroblastic foci), interstitial inflammation and honeycombing, mainly affecting the subpleural areas than the central ones [171]. Generally, UIP is associated with the so-called "temporal heterogeneity", since it is possible to recognize lesions at different stages of development and evolution [168]. UIP has a phenotype similar to idiopathic pulmonary fibrosis (IPF); these diseases seem to share a common gain-of-function mutation of the mucin 5B promoter (MUC5B) [172,173]. The latter, secreted by submucosal mucinous gland cells, has a key role in mucosal ciliary function, regulating local immune responses and influencing alveolar regeneration following injuries [174]. A specific variant of the MUC5B promoter (rs35705950) has been shown to be the strongest genetic risk factor for IPF, since it is observed in at least 50% of patients and has also been described as a strong risk factor for RA-associated ILD, especially in patients with a UIP pattern of the disease [172,173,175].

The features of NSIP are diffuse and spatially homogeneous including bilateral, patchy areas of ground-glass opacities of the lower lobes, subpleural sparing, areas of consolidation, irregular linear opacities, thickening of bronchovascular bundles and bronchiectasis, but without honeycombing [176,177,178,179].

OP is characterized by granulation tissue buds, the so-called "Masson bodies", within alveolar ductus, alveoli and bronchioles, which could obstruct the airways. The involved tissues contain pro-inflammatory cells, fibrin, myofibroblasts, and immature connective tissues [180]. This pattern may be primarily due to RA but also it could be secondary to drug hypersensitivity. In fact, it has been reported following therapies with rituximab, MTX, etanercept, and sulfasalazine [181,182,183].

LIP is a benign lymphoproliferative disorder which is histologically characterized by a diffuse, polyclonal interstitial infiltrate of lymphoid cells [184,185]. Such infiltrate may organize in germinal center-like structures and lead to the thickening of alveolar septa. Interestingly, LIP may be detected not only in RA, but also in other autoimmune diseases, such as Sjogren's syndrome, Hashimoto's thyroiditis, and SLE [186].

DIP is related to an extensive accumulation of intra-alveolar pigmented macrophages in the distal airspaces of the lung, sometimes associated with giant cells [187]. Lung biopsy allows the diagnosis of DIP. This complication of RA is generally associated with tobacco smoking habit, even if approximately 10–42% of patients with DIP are nonsmokers [188]. Moreover, DIP may also be secondary to the occupational exposure and drugs [189,190].

DAD is another ILD pattern observed in RA, which consists of an acute exudative phase and a late proliferative or reparative one. The exudative phase, characterized by alveolar and interstitial edema and formation of hyaline membranes, is the most prominent in the first week following the lung injury. Subsequently, after 1 or 2 weeks, the reparative phase occurs, due to the proliferation of type II pneumocytes and interstitial fibrosis [191]. Depending on the severity of the injury, fibrosis may significantly improve, remain stable, or progress to honeycombing lung, worsening the patient's prognosis. It has been also reported that DAD could be associated with a reaction to some drugs, including leflunomide, bleomycin, busulfan, cyclophosphamide, melphalan, and gold salts [192].

FB also known as hyperplasia of the bronchial associated lymphoid tissue (BALT) or bronchiolar nodular lymphoid hyperplasia, is a rare clinical entity characterized by the development of lymphoid follicles with germinal centers in the peribronchial areas of the small airways. It is codified, together with LIP, among the so-called reactive lymphoproliferative pulmonary diseases. This kind of pattern may be observed in several clinical settings, like immunodeficiency states, autoimmune diseases, infections, obstructive airway diseases [193,194].

5.2.3. *Clinical manifestations of RA-ILD*

Paradoxically, despite the extension of lung involvement, RA patients with ILD may remain asymptomatic for a long time. In fact, RA-ILD develops insidiously and may be present and asymptomatic. When present, the most common symptoms include the shortness of breath, especially after exertion, and the dry non-productive cough. Progressive dyspnea is mainly due to exertional hypoxemia and increased dead space ventilation [195,196,197]. Loss of appetite, fatigue and weakness, unexplained weight loss, may also be recognized in the clinical picture. In early disease, the clinical examination may be negative, but

tachypnoea and fine bibasal inspiratory crackles are common [153,198]. In this context, the patient's rheumatoid joint disease may limit their ability to exercise sufficiently to precipitate exertional dyspnea and by the presence of generalized fatigue due to systemic inflammation.

5.2.4. Diagnosis of RA-ILD

HRCT is the method of choice to assess the lung involvement if the clinical suspicion of RA-ILD is present, particularly in early disease and especially for UIP and NSIP. In fact, affected patients could not have some abnormalities on conventional radiographs of the chest [199]. HRCT accuracy has been reported to be about 70% when compared with the histological diagnosis [129]. Biopsy should be still performed in cases of atypical HRCT findings to exclude infection and to discern UIP and other RA-ILD subtypes in non-responder patients to conventional therapies [130].

Pulmonary function tests (PFTs) are also recommended. PFTs typically show a restrictive pattern and a diffusion impairment. In fact, a defect in DLCO is common as an early sign on PFTs finding in RA-ILD [200]. A 6-min walking test may be of some usefulness [201]. Bronchoalveolar Lavage (BAL) may play an important role in the evaluation of alternative diagnosis to RA-ILD, including diffuse alveolar hemorrhage, opportunistic infections and drug toxicity. It is not routinely used as a diagnostic tool in the clinical practice, since BAL changes are not RA-ILD specific [202].

5.2.5. Therapies

Presently, no consensus therapeutic guidelines have been established to guide the clinicians in the clinical management of RA-ILD. Usually, GCs represent the first-line therapy of newly diagnosed RA-ILD, initiated with oral prednisone at a daily dose of 0,5–1 mg/kg. GCs are used for prolonged period with a subsequent gradual tapering based on the clinical response [203]. OP and NSIP seem to better respond to GCs, whereas patients with UIP are less likely to respond [204]. In non-responder patients, GCs may be associated with some immunosuppressive drugs, such as azathioprine, cyclosporine, and cyclophosphamide [205,206]. Rapidly progressive or extensive disease with arterial hypoxemia is often treated with either daily oral or monthly intravenous cyclophosphamide in combination with GCs [205]. Furthermore, mycophenolate mofetil (MMF) has been shown to have a beneficial effect on connective tissue disease (CTD) – ILD, considering its additional action on fibroblasts, endothelial cells, and smooth muscle cells [205,207]. In a study of 125 patients with CTD related ILD treated with MMF, in a subgroup analysis of 18 patients with RA- ILD, it has been identified a trend toward the improvement of forced vital capacity, following the initiation of therapy [208,209,210]. Some refractory CTD-ILD have been successfully treated with rituximab, although larger prospective studies are needed to validate these findings in patients with RA-ILD [211,212]. TNF inhibitors should be used with caution in these patients according to reports of increased rates of lung toxicity with these agents [213,214]. However, a prospective observational study of 367 patients with RA-ILD showed no increase in mortality following treatment with anti-TNF agents compared with standard immunomodulatory agents [215]. These observations suggest the need of further studies to fully evaluate the efficacy and the safety of bDMARDs on RA-ILD.

5.3. Pleural involvement in RA

Pleural effusion, pleuritis and pleural nodules are the most common forms of RA pleural disease, whereas pneumothorax is a rare manifestation [216,217,218]. Pleural thickening and scarring may be observed as a late manifestation of recurrent, severe and untreated pleuritis. Symptomatic RA-associated pleural involvement is rare with an overall incident rate of 3–5%, however, in postmortem studies pleural involvement is described in almost 70% of patients [216,218,219].

Pleural effusion has a male preponderance, with more than 80% of cases reported in adult men with high sera levels of RF [219]. The possible causes are previous infections, local production of immune complexes, chronic inflammation with cytokine release and activation of fibrosis, and an impaired resorption of fluid due to its high protein content. Furthermore, the rupture of subpleural nodules may occur, leading to inflammation-induced capillary leak and obstruction of lymphatic drainage [218,219]. Effusions are more commonly unilateral with left predominance, but also bilateral and migratory effusions are described [219]. If symptomatic, RA patients usually complain fever and chest pain. The initial evaluation of RA pleural effusion includes chest radiograph, showing blunting of the costophrenic angles. Smaller effusions may be detected with lateral and decubitus films. Ultrasound is useful to evaluate the characteristics of the fluid, which may be loculated and complex, and to guide needle aspiration. In fact, thoracentesis should be performed for any pleural effusion >1 cm on decubitus imaging [219]. A "rheumatoid effusion" is usually an exudate presenting low pH, low glucose, and elevated lactate dehydrogenase levels [216,218]. In cases of chronic pleural inflammation, the fluid may appear as "pseudochylous", due to the presence of cholesterol crystals in the fluid, which generally differs from a true chylothorax by the absence of triglycerides and/or chylomicrons [220].

Usually these pleural effusions may resolve spontaneously within several weeks or with management of RA. If small and asymptomatic, no therapy is indicated; however, longstanding pleural inflammation may result in pleural thickening, trapped lung and possible infections. In patients with large and symptomatic effusions, thoracentesis, instillation of intrapleural GCs or systemic GCs, fibrinolytic agents may be considered as therapeutic options [221].

5.4. Caplan syndrome

Caplan syndrome or rheumatoid pneumoconiosis is a rare syndrome, first described in 1953 by Caplan on coal miners of South Wales with RA [222,223]. It generally occurs in patients with chronic exposition to coal, silica and/or asbestos and underlying RA disease. In fact, the association between long exposure to silica, pneumoconiosis, and RA has been shown [224]. The prevalence of the disease is extremely variable, from 0.75% to 1.5%, depending on different distribution of minerals in different geographic areas and work conditions [225,226].

The exact pathogenic mechanism is not completely understood but may reflect autoimmunity induced by inhalational exposures [227]. In fact, it has been proposed that RA predisposes to pneumoconiosis and viceversa [224]. In addition, RF is more frequent in patients with Caplan syndrome compared with exposed miners with or without pneumoconiosis [228]. Similarly, ACPA were also found in Caplan syndrome, and there is a link between exposure to silica and antibodies against citrullinated proteins- positive RA [229].

By conventional chest radiographs, this syndrome is associated with multiple well-defined rounded opacities, ranging in size from 0.5 to 5.0 cm, and distributed throughout both lung fields, but predominantly at the periphery. These lesions may appear in crops, occasionally coalesce and form a larger confluent nodule, many of which are cavitary or calcified [225]. Histologically, the nodules in Caplan syndrome are similar to necrobiotic ones. In particular, central necrotic area is surrounded by alternate layers of black coal dust and necrotic tissue. If a layer of inflammatory cells, mainly polymorphonuclear granulocytes and macrophages, is present, the nodule may be defined as rheumatoid; otherwise, it may be codified as a silicotic one [230]. The occupational anamnesis in RA associated with radiological opacities is of importance in differentiating Caplan syndrome from other rheumatoid pulmonary lesions [231].

Generally, the pulmonary nodules in Caplan's syndrome are asymptomatic and the diagnosis may be incidental by conventional chest radiograph. Since this condition is usually asymptomatic, it could not require a specific therapy unless a complication develops, such as the

rupture of a cavitating lesion into the pleural space [232]. No specific therapeutic strategy is available; thus, the treatment should be individually evaluated [222]. Generally, as well as other pneumoconioses, silicosis does not respond to medical treatment [225]. Usually, cs- and bDMARDs do not alter the evolution of pulmonary nodules, but GCs have been reported of some usefulness in some patients with compressive or rapidly growing lesions [233,234].

6. Discussion and conclusions

RA is an inflammatory disease typically affecting the joints, but the systemic inflammatory process may involve other tissues and organs. Many extra-articular manifestations are recognized, which are related to worse long outcomes, in particular with the functional impairment and the increased mortality [235]. Nodules are the most common extra-articular feature, which are found in about 30% of patients. Secondary Sjögren's syndrome and pulmonary manifestations are observed in almost 10% of patients, also in early disease [235]. Although it has been suggested that some extra-articular manifestations may occur less frequently [236], active RA with high disease activity has been associated with an increased risk of such features [36,70,103]. Male gender, smoking habit, severe joint disease, worse function, high pro-inflammatory markers levels, high titer of RF, and HLA-related shared epitope have been reported as clinical predictors of occurrence of these rheumatoid complications [7,22,27,54]. On these bases, patients with these characteristics should be carefully assessed and folled-up. In addition, there is a little evidence deriving from randomized controlled trials in this field, thus the therapeutic strategy is mainly empiric and based on small case series and retrospective studies [89,120,182]. However, considering that these extra-articular manifestations are usually related to the more active and severe RA, an aggressive therapeutic strategy is usually employed in view of the poor outcomes of these patients [15,40,212,236].

Recently, the usefulness of personalised medicine principles has been proposed on RA [237,238]. These claim a clinical therapeutic approach based on individual variability in genes, environmental exposure, and lifestyle [239,240,241]. In fact, the main target is to tailor the treatment strategy according to patient characteristics in choosing the right treatment and a better timing of administration, in order to maximize the efficacy and reduce the possible drug toxicities [239,242]. In this context, the need for biomarkers facilitating early diagnosis and profiling those individuals at the highest risk for a poor outcome has become of crucial interest to improve these unmet needs [243,244]. Thus, the application of precision medicine in rheumatic diseases is suggested to improve the outcomes of these patients [245,246,247]. Taking together these observations, future studies are advocated to link the patient phenotypes in view of extra-articular manifestations to possible targeted therapies.

In conclusions, the extra-articular features of RA remain, despite the improvement of joint damage, a major diagnostic and therapeutic challenge, since these are associated with a poor prognosis and need to be early recognized and promptly managed. Future specific designed studies are necessary to fully evaluate the pathogenetic mechanisms of such complications and possible targeted therapeutic strategies to improve the long-term outcomes of these patients.

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