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Rheumatologic complications of CAR-T Cell therapy. Experience of a single center

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ABSTRACT

Introduction: Chimeric Antigen Receptor T-cell (CAR-T) therapy has emerged as a promising treatment for hematological malignancies. However, its association with immune-related complications such as rheumatic complications, is not well defined.
Methods: We conducted a retrospective study to analyze rheumatic complications in 310 patients treated with CAR-T therapy at a single center from January 2020 to May 2024.
Results: We identified six patients (1.9 %) who developed rheumatic complications, including rheumatoid arthritis (RA)-like manifestations with biopsy-proven nodules, palindromic rheumatism, myositis, necrotizing fasciitis, and osteonecrosis (ON). Symptoms appeared between 2 to 11 weeks after therapy, with inflammatory arthritis manifesting later. Notably, 2 patients developed RA-like arthritis with subcutaneous nodulosis, while others presented with transient arthritis flares, severe soft tissue and joint involvement, such as pseudo-podagra and ON. Imaging findings and biopsies confirmed the diagnoses. Treatment included glucocorticoids, hydroxychloroquine, and nonsteroidal anti-inflammatory drugs, with variable responses.
Conclusions: Clinicians should be aware of these potential complications to ensure prompt diagnosis and management. Further research is needed to elucidate the mechanisms underlying these autoimmune phenomena and to establish standardized treatment protocols.

Introduction

Chimeric antigen receptor T-cell (CAR-T) therapy is approved treatment for refractory leukemia, lymphoma and multiple myeloma among others and a promising treatment for a range of systemic autoimmune diseases, such as systemic lupus erythematosus (SLE), systemic sclerosis, and antisynthetase syndrome, among others [1]. Several immune-mediated complications are known to occur following CAR-T cell therapy, including cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and various skin diseases. However, post-CAR-T cell rheumatological complications are not well understood, with only one case of palindromic rheumatism (PR) reported by our group [2].

Methods

Cases treated with CAR-T cells from January 2020 to May 2024 at a single center were analyzed. Patients treated with second-generation

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CAR-T products targeting CD19 (ARI-0001 or varnimcabtagene autoleucel, with scFv derived from the A3B1 mAb) and BCMA (ARI-0002h or cesnicabtagene autoleucel, with scFv derived from the humanized J22.9 mAb) were assessed. Most of the patients were treated for hematological disorders. None of the patients had an underlying systemic autoimmune disease as the cause for CAR-T cell therapy.

ARI-0001 and ARI-0002h were authorized in 2021 and 2024, respectively, by the Spanish Drug Agency (AEMPS) under the Spanish Royal Decree 477/2014, transposed from the European Regulation [EC] No 1394/2007, commonly known as the "Hospital Exemption" clause (HE), amending Directive 2001/83/EC and Regulation [EC] No 726/2004, particularly focusing on Article 17 of Regulation (EC) No 1394/2007 for ATMPs (Advanced Therapy Medicinal Products). Both ARI-0001 (targeting CD19) and ARI-0002h (targeting BCMA) are point-of-care ATMPs based on engineered T-cells transduced with lentiviral vectors. Authorization for use under HE was obtained based on the results of clinical trials NCT03144583 for B-Acute Lymphoblastic Leukemia (B-ALL) [3] and NCT04309981 for Multiple Myeloma [4].

Results

During the study period, 310 patients were treated with CAR-T cell therapy, including 180 with anti-CD19 and 130 with anti-BCMA. Rheumatologic complications occurred in only 6 patients (1.9 %), of whom 4 were male. The mean age at the time of the rheumatic manifestation was 47.3 years (range 24–59 years), and the mean time to onset was 5.5 weeks (range 2–11 weeks). The underlying diagnoses for CAR-T cell therapy were acute B-lymphoblastic leukemia (3 cases), chronic lymphocytic leukemia (1 case), follicular lymphoma (1 case), and IgD-Kappa IIb multiple myeloma (1 case).

Three out of six patients died after CAR-T cell therapy (due to severe systemic infections), with a mean survival time of 25.9 months. Three patients remain alive with good control of their underlying disease after a mean follow-up of 17.6 months.

Table 1
Clinical characteristics and outcomes of patients with Rheumatic complications of CAR-T Cell therapy.

Case	Sex	Age	Underlyng diagnosis	Previous treatments	Type of CAR-T Cell	CRS/ Grade	CRS Treatment	Cutaneous Complications	Rheumatic complications	Time to onset (wks)	Treatment	Evolution	Alive
1	M	58	Chronic lymphatic leukemia	Fludarabine CYC Mitoxantrone Vincristine, Ofatumumab Ibrutinib RTX venetoclax R-CHOP Epcoritamab	CD19	Yes/1	TCZ		RA-like with biopsy proven rheumatoid nodules	8	PDN HCQ	Ongoing	Yes
2	M	59	Follicular lymphoma	R-CHOP Etoposide MPDN R-ESHAP Epcoritamab	CD19	Yes/1	TCZ		RA-like with biopsy proven rheumatoid nodules	4	PDN HCQ	Ongoing	Yes
3	F	58	Acute B Lymphoblastic Leukemia	PETHEMA-LLA-AR protocol**	CD19	No	None	GVHD-like reaction	Severe toe soft tissue infiltration (Pseudo-podagra)	2	PDN	Partial response	No
4	F	30	Acute B Lymphoblastic Leukemia	PETHEMA-LLA-AR protocol**	CD19	Yes/1	TCZ Anakinra		Myositis with Necrotizing fasciitis Femoral avascular necrosis*	2	PDN	No response	No
5	M	24	Acute B Lymphoblastic Leukemia	Daunorubicin Asparaginase CYC Idarubicin Fludarabine Cytatabine Allogenic SC transplant	CD19	Yes/1	TCZ		Ankle osteonecrosis plus periarthritis	5	NSAID PDN	No response	No
6¥	F	55	IgD Kappa multiple myeloma	Doxorubicin Bortezomib Autologous SC transplant Lenalinomide Daratumumab Pomalidomide CYC Dexametasone	BCMA	Yes/1	TCZ		Palindromic rheumatism	4	None	Resolution	Yes

CRS: Cytokine release syndrome, CYC: Cyclophosphamide, GVHD: Graft-versus-host disease, HCQ: Hydroxychloroquine, MPDN; Methylprednisolone, PDN: Prednisone, RA: Rheumatoid arthritis, RTX: Rituximab, R-CHOP: RTX plus CYC, doxorubicine, vincristine, prednisone, ST: Stem cell, TCZ: Tocilizumab

¥ Previously published (Gómez-Puerta JA et al. Rheumatology 2024 Jan 23:keae046)

* We cannot determine the timing of the osteonecrosis, as it may have been present beforehand with the patient remaining asymptomatic

** Therapeutic regime for Acute B Lymphoblastic Leukemia from Spanish Society of Heamatology and hemostasis. Ahttps://www.fundacionpethema.es/sites/default/files/protocolos/Protocolo%20LAL_2019_febrero%202023.pdf

The main rheumatic syndromes included inflammatory arthritis, with two cases of rheumatoid arthritis (RA)-like symptoms accompanied by biopsy-proven nodulosis (2 cases), and one case of palindromic rheumatism (PR). Other diagnoses included ankle osteonecrosis with periarthritis, severe myositis with necrotizing fasciitis, and a severe inflammatory soft tissue reaction in the toe (pseudo-podagra). Systemic and localized reactions were observed during the first weeks (mean 3.0 weeks), while inflammatory arthritis appeared after a mean period of 2 months.

Here, we describe in detail 5 cases of rheumatic complications following CAR-T cell therapy, including clinical manifestations, imaging findings, treatment, and follow-up. The main characteristics are summarized in Table 1. Details of the previously published case with transient PR are also provided in Table 1 as case 6 [2].

Case 1

A 58-year-old Caucasian male with a past medical history of chronic lymphocytic leukemia (B-CLL) transformed into aggressive lymphoma (Richter syndrome) had received multiple lines of treatment, all discontinued due to inefficacy or side effects (see Table 1). He underwent anti-CD19 CAR-T therapy (ARI-0001) in January 2024, experiencing grade 1 CRS treated with tocilizumab, without ICANS. He denied any family history of autoimmune diseases or personal history of hyperuricemia or psoriasis.

Two months after CAR-T therapy, he developed thickening and lesions in the subcutaneous tissue of his right wrist and right elbow, accompanied by bursitis. He also reported neuropathic pain on the inner side of the 4th finger and, to a lesser extent, in the 1st, 2nd, and 3rd fingers.

On physical examination, there was thickening in the right wrist with mild flexor tenosynovitis, right elbow bursitis, and subcutaneous (SC) nodules in the forearm (Fig. 1A). No tophi or synovitis were observed. Ultrasound assessment revealed hypoechoic nodular lesions up to 100 mm, poorly defined and without Doppler signal, along with smaller similar lesions on the radial dorsal and ulnar volar margins of the wrist, as well as vascular dilations without thrombophlebitis. MRI of the wrist showed tenosynovitis of the wrist flexors.

A skin biopsy of the SC nodule revealed deep reticular dermal edema and a focal lymphoplasmacytic inflammatory infiltrate around the blood vessels within the hypodermis. The central area exhibited fibrinoid necrosis, surrounded by lymphocytes and histiocytes, along with the formation of isolated granulomas (Fig. 1B). No signs of vasculitis were observed. ESR and CRP levels were normal, as were uric acid levels. Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP) antibodies were both negative. After 3 months of treatment with

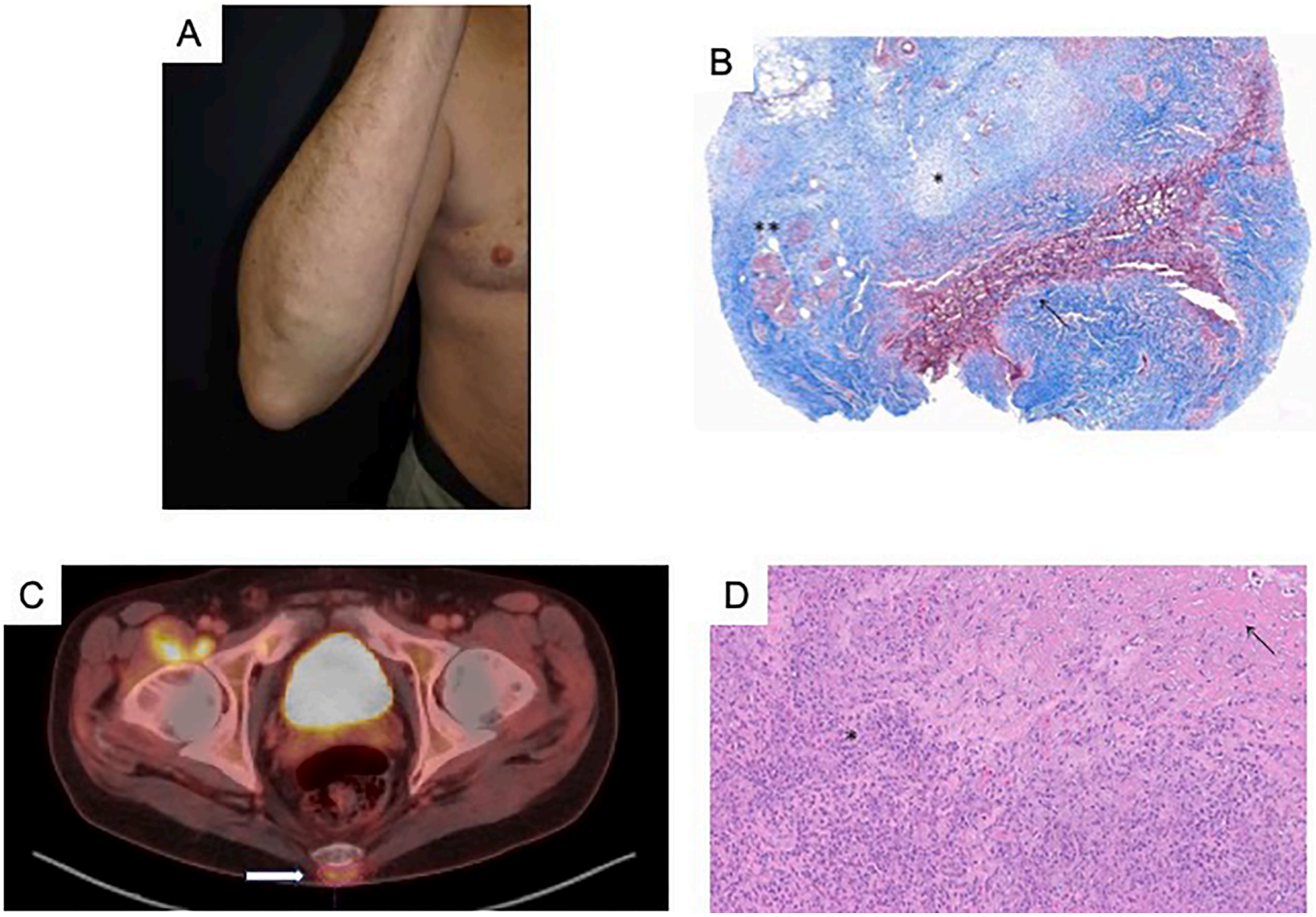

Fig. 1. Subcutaneous nodules

Figure 1A. Subcutaneous nodules extending along the right forearm, Figure 1B (Case 1). Histological section of skin stained with Masson's trichrome (x100). Edema (*) and a focal lymphoplasmacytic inflammatory infiltrate around the blood vessels were observed in the deep reticular dermis. A central area of fibrinoid necrosis (arrow), surrounded by lymphocytes and histiocytes with the formation of isolated granulomas (**) was identified in the hypodermis. No signs of vasculitis were seen. PET/CT scan with focal uptake of FDG in retrococcygeal soft tissues, Figure 1C. The findings were consistent with rheumatoid nodule, Figure 1D (Case 2). Hematoxylin and eosin stained section of skin, showing in the deep dermis and hypodermis, a central area of necrosis with a fibrinoid appearance (arrow), surrounded by lymphocytes and histiocytes (*) without granuloma formation. No evidence of vasculitis or mucin deposits were observed (x200).

hydroxychloroquine (200 mg/day), the patient is asymptomatic, with only two small, non-tender SC nodules remaining in his forearms.

Case 2

A 59-year-old Caucasian male with a family history of psoriasis and an underlying diagnosis of grade 3a stage IV-B follicular lymphoma (with hepatic and bone marrow involvement), refractory to multiple lines of treatment (see Table 1), underwent anti-CD19 CAR-T therapy (ARI-0001) in July 2023, resulting in a complete metabolic response, as confirmed by the latest PET/CT scan.

One month after CAR-T cell infusion, the patient experienced pain in the right wrist, accompanied by edema and morning stiffness, which later resolved. Subsequently, he developed joint pain in both elbows and knees, along with the appearance of nodular lesions on the elbows, knees, and coccygeal region (Fig. 1C). He occasionally complained of joint effusion in both knees.

The patient was taking NSAIDs with partial relief. Five months later, there was transient improvement in the pain, but the symptoms reappeared one week ago. He denied uveitis, diarrhea, heel pain, or oral or genital ulcers.

On physical examination, there was mild joint effusion in the right knee and SC nodular lesions on both elbows and the coccygeal area, rubbery in consistency, firm but not stony. He also had red palms but no psoriasis lesions. Arthrocentesis yielded 5 cm^3 of amber-yellow, non-purulent fluid with 3800 leukocytes/mm^3 and no crystals. RF and CCP antibodies were both negative as well as acute phase reactants. X-rays of the knees and hands showed no structural lesions.

A skin biopsy of an SC nodule showed preserved epidermis. In the deep dermis and hypodermis, there was a central area of necrosis with a fibrinoid appearance, surrounded by lymphocytes and histiocytes, without granuloma formation. No evidence of vasculitis or mucin deposits was observed (Fig. 1D).

The patient was diagnosed with RA-like arthritis with rheumatoid SC nodules. Four months after symptom onset, he continued to experience inflammatory arthralgias, predominantly in the knees, without the appearance of new nodules. In collaboration with the Hematology department, treatment with hydroxychloroquine (200 mg/day) and low doses of glucocorticoids was initiated, resulting in good symptom control.

Case 3

A 58-year-old Caucasian woman with a history of hypothyroidism, gastric bypass for severe obesity, and hyperuricemia with one episode of podagra was diagnosed in March 2018 with pro-B acute lymphoblastic leukemia (B-ALL) with central nervous system infiltration and t(8;14) cytogenetics. She underwent induction therapy according to the Spanish Society of Hematology and Hemostasis protocol (PETHEMA-LLA-AR), achieving complete remission (CR) with positive minimal residual disease (MRD+) (> 0.1 %). Therefore, she was rescued with IDA-FLAG therapy, subsequently achieving CR with negative MRD. She continued with consolidation therapy under the PETHEMA-LLA-AR protocol.

In April 2020, she received anti-CD19 CAR-T cell therapy (ARI-0001) as part of a clinical trial. Two weeks later, she reported pain and swelling in the first toe of her left foot, resembling previous gout episodes. She had been on intermittent allopurinol treatment. Physical examination revealed swelling in the first toe of the left foot, with bruising along the phalanx. No signs of arthritis were present in other joints (Fig. 2A). Uric acid levels were normal. An X-ray of the left foot showed increased thickness of soft tissue in the first toe without erosions (Fig. 3A). Ultrasound showed soft tissue swelling in the first toe, also without erosions (Fig. 3C).

Over the following two months, the patient experienced a progressive increase in pain and edema in the periarticular tissues of the first toe, accompanied by erythema, warmth, and necrosis of the surrounding area. MRI revealed a large solid soft tissue lesion with a neoformative appearance surrounding the proximal phalanx of the first toe and infiltrating the tendon, muscle, fatty tissue, and subcutaneous planes (Fig. 3B). The lesion had a lobulated morphology with irregular margins, measuring 41 × 58 × 59 mm. It exhibited a low signal on T1 and a high-

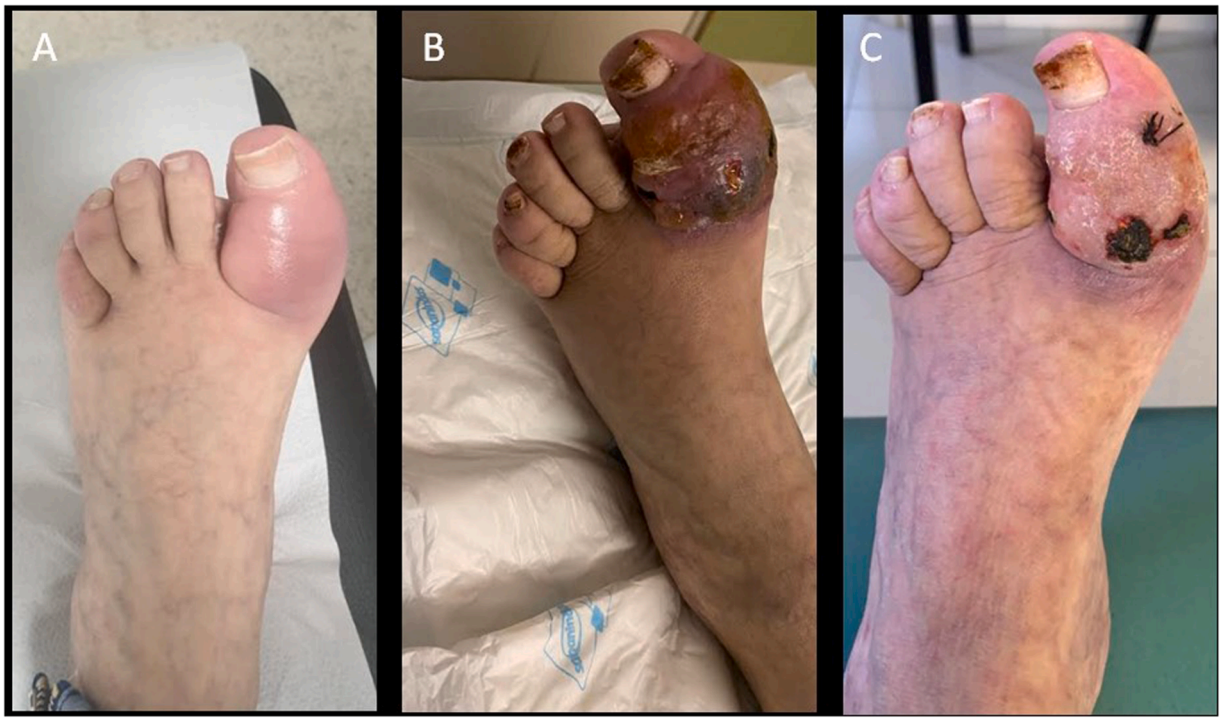

Fig. 2. Clinical evolution of Pseudo-podagra (Case 3).
A. At onset. B Six weeks later, C. Eight weeks later

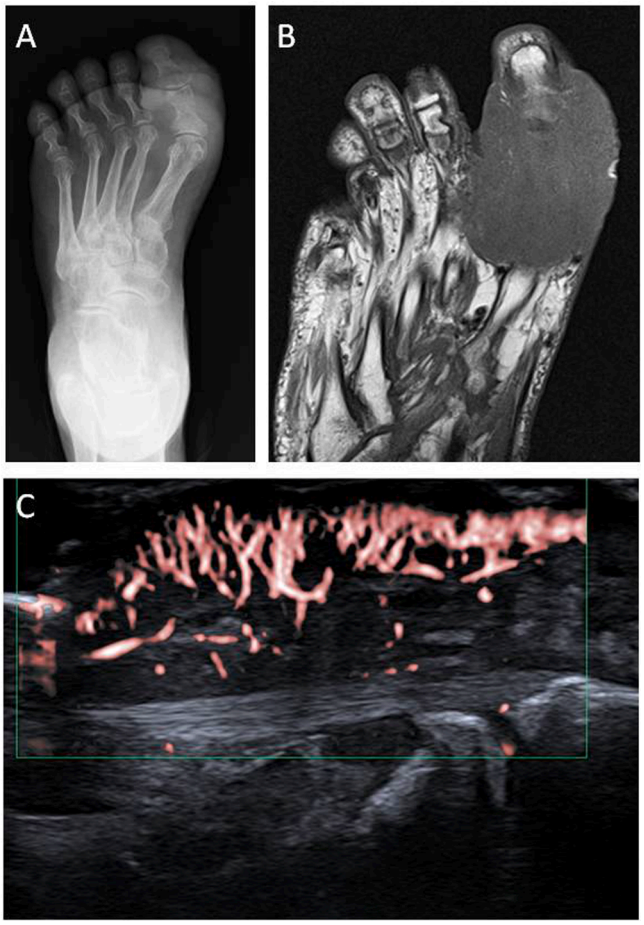

Fig. 3. Imaging findings (Case 3).
A. X-Ray: Soft tissue edema in the first toe without evidence of erosions.B. MRI: large solid soft tissue lesion with a neoformative appearance, surrounding the proximal phalanx of the first toe and infiltrating the tendon-muscle, fatty, and subcutaneous planes, C. Ultrasound: Proximal phalanx with heterogeneous echostructure, poorly defined contours, and areas of increased vascularization on Doppler imaging

intermediate signal on DP/T2, with a heterogeneous pattern showing intense diffuse contrast enhancement, along with non-enhancing cutaneous foci consistent with ulcerations and blisters. Additionally, the proximal phalanx showed signs of infiltration, with altered signals—predominantly hypointense on T1 and isohyperintense on T2—with a heterogeneous pattern and significant enhancement.

Six weeks later, the edema worsened, with hyperpigmentation and the appearance of necrotic skin lesions around the first toe (Fig. 2B).

A skin punch biopsy showed a hyperplastic epidermis with hyperkeratosis and a serous exudate crust, associated with numerous necrotic keratinocytes, mild spongiosis, and lymphocytic exocytosis. In the dermis, there was a dense lymphoid infiltrate affecting the entire dermis represented in the sample. The lymphoid infiltrate expressed CD3, CD2, and CD5 with partial loss of CD7 expression. Stains for CD79a, CD19, TdT, CD10, and CD34 were negative. A deeper biopsy, including soft tissues, revealed scattered necrotic tumor cells mixed with the atypical T-cell infiltrate. In conclusion, findings were consistent with atypical T-cell lymphoid hyperplasia, without evidence of viable tumor infiltration.

Low doses of corticosteroids and local measures were administered, resulting in progressive improvement over the following weeks (Fig. 2C). During follow-up, there were no new episodes of edema or pain in the big toe or in other locations. Unfortunately, the patient passed away in October 2021 due to severe pneumonia

Case 4

A 30-year-old Mestizo woman with B-ALL BCR was diagnosed in July 2021 without central nervous system involvement. She was treated with the PETHEMA-LLA-AR protocol for one year, with primary failure. In January 2024, she was admitted for anti-CD19 CAR-T cell therapy (ARI-0001). As a complication, she developed persistent grade 2 CRS, which required three doses of tocilizumab, and hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS), treated with anakinra.

Two weeks later, she complained of severe pain in her lower limbs. A CT scan revealed slight asymmetric thickening with heterogeneous contrast uptake of some muscle bellies in the anterior and medial compartments of both femoral regions. Notably, there was asymmetric thickening of the right sartorius muscle and the distal third of the medial vastus muscle of the left quadriceps. Additionally, diffuse thickening of the deep muscular fasciae, as well as diffuse trabeculation of the subcutaneous fat and intermuscular planes, were observed. No dense basal areas suggesting hematomas or air bubbles were present. The findings were suggestive of bilateral myositis in the anterior and medial compartments, with an associated component of necrotizing fasciitis. Unfortunately, the patient's instability did not allow for an MRI to be performed.

Additionally, there was an alteration in bone density at the level of both femoral condyles and tibial plateaus in the form of geographic areas of hypodensity with sclerotic margins, suggestive of avascular osteonecrosis (ON) in these locations.

The patient developed rhabdomyolysis (serum creatine kinase levels peaked at 26,889 U/L, with normal values at admission) with acute renal failure, which progressed with a torpid evolution. This led to multiorgan dysfunction, including renal failure and anuria refractory to diuretic treatment with furosemide infusion, fulminant hepatic failure, cardiovascular dysfunction with refractory vasoplegia, and moderate left ventricular dysfunction that did not respond to maximum vasopressor and inotropic support. She also presented with metabolic acidosis refractory to continuous bicarbonate treatment, as well as refractory hyperkalemia, hypocalcemia, and increasing hyperlactatemia. Continuous veno-venous hemodialysis (CVVHD) with hemoperfusion was initiated, and additional ventilatory support was provided due to respiratory distress. However, the patient passed away days later.

Case 5

A 23-year-old Mestizo male patient with a history of refractory B-ALL to multiple therapeutic regimens (see Table 1), including allogeneic hematopoietic stem cell transplantation, received treatment with anti-CD19 CAR-T therapy in April 2020. He developed grade 1 CRS one day after the infusion, which was treated with tocilizumab.

Five weeks later, he was admitted with a 7-day history of right ankle joint pain, accompanied by functional impairment, erythema, and increased local temperature. Upon assessment, the patient presented with erythema over the right external malleolus (Fig. 4A), tenderness on palpation in the tarsus region, external malleolus, and Achilles tendon, along with pain during mobilization of the subtalar joint. An X-ray of the ankle showed increased opacity of the talar dome (sclerosis), suggestive of ON (Fig. 4B). An ankle ultrasound revealed a moderate amount of peritendinous fluid around the posterior tibial tendon without increased vascularization, suggestive of tenosynovitis, and joint effusion in the anterior tibio-talar joint, also without increased vascularization. An MRI of the ankle showed a lesion with heterogeneous signal intensity, containing areas of both low and high T1-T2 signal intensity, with well-defined geographic borders measuring 32 × 31 × 14 mm. It was located in the subchondral area of the talar dome and showed irregularities of the articular surface, compatible with signs of partial collapse (Fig. 4C). There was perilesional edema due to mechanical overload and reactive changes in the rest of the talus.

A PET-CT scan showed increased FDG uptake in the talar dome,

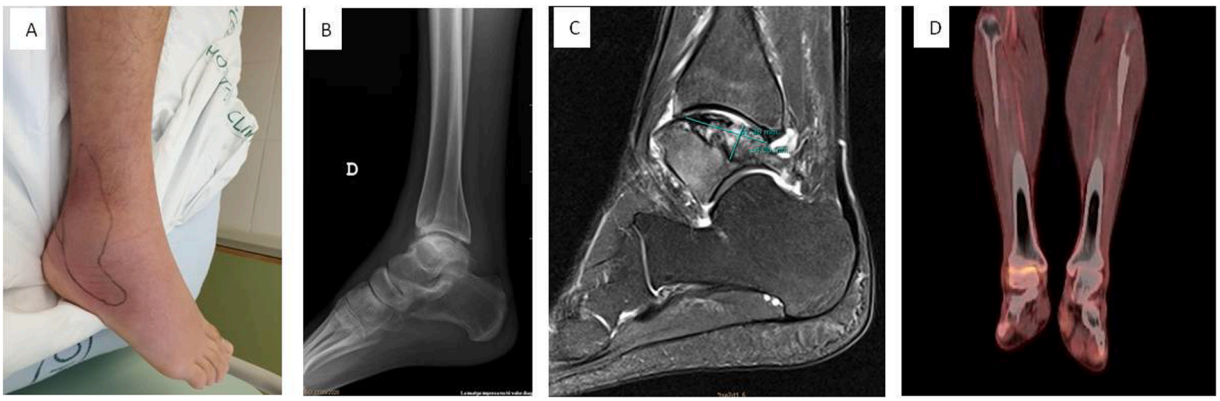

Fig. 4. Case 5, Right ankle osteonecrosis. A. Clinical aspect, B. X rays, C. MRI, D. PET/CT scan.

consistent with the findings of the bone scan, the collapse observed on MRI, and the fracture noted on the CT scan (Fig. 4D). These findings suggest talar ON rather than an extramedullary infiltration lesion of the underlying condition.

Serology tests for RF, anti-CCP antibodies, and HLA-B27 were all negative. He was treated with a short course of low-dose prednisone and NSAIDs, which led to progressive improvement. Two months after discharge, the patient reported improvement in pain, better gait, and no pain when bearing weight. Unfortunately, 16 months after CAR-T therapy, the patient developed a severe pulmonary infection with respiratory distress and passed away.

Discussion

Rheumatologic complications in patients receiving CAR-T therapy are uncommon. We present here a series of 5 patients treated with CAR-T therapy who developed various rheumatic complications some weeks later. CAR-T-cell therapy is a targeted immunotherapy that utilizes T lymphocytes, collected from either the patient or a donor, which are genetically modified to attack specific tumor antigens. The procedure involves five main stages: 1) white blood cells are removed through leukapheresis; 2) cell enrichment is performed using paramagnetic beads with either a positive (or negative) selection method; 3) T-cells are transduced, after specific T-cell activation, by lentiviral vectors with CAR sequences targeting specific antigens, in these cases CD19 or CD269 (BCMA), using viral (or non-viral techniques; 4) CAR T-cells are cultured and expanded in a medium containing recombinant IL-7 and IL-15 (or other cytokines) and 5) the expanded CAR T-cells are cryopreserved and stored in liquid nitrogen until they are ready for infusion (or infused on fresh without cryopreservation) [3,4].

The exact mechanisms behind the emergence of CAR-T related immune-mediated effects are not known. Most of the available information focuses on immediate complications such as CRS and ICANS. The role of secreted cytokines in CAR-T therapy-related toxicities has been acknowledged since these therapies were first developed. Early research measuring cytokine levels in initial patients revealed extremely high levels of IL-6 and INF-gamma, which prompted the targeted use of cytokine blockade, maily with tocilizumab for IL-6 pathway to treat CRS; in any case the successful treatment of some refractory CRS cases with emapalumab also remarks the role of INF-gamma in the pathogenesis of immune-mediated complications following CAR-T therapy [5]. The monocyte-produced protein IL-1β is involved in the pathophysiology of ICANS, prompting clinical investigations into IL-1 receptor blockade with anakinra [6]. Other data suggest the involvement of other cytokines related to IL-1, such as IL-18, which is associated with the onset of ICANs in pediatric patients who received anti-CD19 CAR-T therapy [7].

Beyond the immune-mediated effects resulting from the release of inflammatory cytokines such as IL-6, IL-1 or IL-18, there are a series of heterogeneous factors, such as the patient's age, the underlying disease, the type of CAR-T, or even the presence of other comorbidities.

CAR-T cells break down cancer cells, releasing tumor-derived antigens that activate the innate immune response and produce high levels of IFN-gamma and IL-6, which promote self-reactive antigen presentation. In particular, in our cases, we hypothesize that those with previous CRS which are dependent on high levels of IFN-gamma and IL-6 would enhance antigen presentation, including the presentation of auto-antigens. This increased availability of antigen could facilitates a strongest immune response, driving the pathogenic mechanisms associated with autoimmunity. In contrast, in our case without CRS (the pseudogout patient), it could involve a greater reliance on elevated levels of IL-1beta [8]. This cytokine plays a crucial role in the pathogenesis of gout, particularly at the level of intrinsic production and additionally, in graft-versus-host disease (GVHD-like) reactions such the one described in this case, where IL-1beta is often present alongside TNF, further underscoring its significance in these inflammatory processes [9].

Apart from the immediate complications of CRS and ICANs, complications in other domains or systems are less well understood. As expected, hematologic manifestations are more common and include immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome due to overactivation of the immune system and characterized by hyperferritinemia, coagulopathy, hepatic dysfunction and cytopenias among others [6].

Skin toxicities from CAR-T therapy commonly present as maculopapular rash, papules, purpura, urticarial rash, oral mucositis and bullous eruptions among others. For instance, Hu et al, reported high levels of IL-6 and IFN-γ in bullous fluid lesions induced by CAR-T [10]. Oftalmological complications include blurred vision and vision loss and optic neuropathies [11].

There are no previous reports of rheumatic complications beyond the case reported by our group some months ago [2]. This case involved a patient with multiple myeloma who received CAR-T BMCA therapy and developed episodes of PR that began one month after the therapy, persisted for three months, and were even confirmed by ultrasound with Doppler signal. The episodes eventually resolved without the need for DMARD treatment.

Here we describe 5 additional cases, all developing clinical symptoms among 2–8 weeks of receiving CAR-T cell therapy.

Special attention should be given to the two seronegative RA-like cases with rapid onset biopsy proven subcutaneous rheumatoid nodules, which improved with low doses of corticosteroids and hydroxychloroquine. This phenomenon had not been previously described and opens the door for clinicians who monitor and follow patients exposed to CAR-T therapy to watch for similar immune-mediated phenomena.

We acknowledge that this is a paradoxical phenomenon, as even

recently, the first case of a patient with RA treated with CAR-T therapy was published [12]. One possible explanation is that pro-inflammatory cytokines, endothelial markers, and angiogenic factors, which are closely linked to the pathogenesis of RA and contribute to inflammation, vascular changes, and immune dysregulation [13–15], were induced by CAR-T therapy. Notably, our center has reported that some of these markers, including soluble TNF receptor 1, angiopoietin-2, and soluble VCAM-1, are significantly elevated in patients with CRS and/or ICANS following CAR-T cell infusion [16]

Rheumatoid nodules typically appear in patients with seropositive RA and advanced disease, often alongside other extra-articular manifestations such as interstitial lung disease [17]. Although rheumatoid nodules are highly characteristic of RA, they can also occur in other autoimmune rheumatic diseases such as SLE and Sjögren's syndrome [18] .

The limited number of cases does not allow us to draw definitive conclusions and calls for caution when attributing causality of CAR-T therapy in triggering immune reconstitution weeks after treatment and inducing inflammatory arthritis, similar to what is observed with immunotherapies, particularly checkpoint inhibitors [19].

There have been previous reports of necrotizing fasciitis following bone marrow transplantation [20–23]. However, no cases have been described following CAR-T therapy. Conditions that compromise the immune system, such as diabetes, chronic kidney disease, cancer, or steroid use, can increase the risk of developing necrotizing fasciitis. Additionally, intravenous drug use, recent surgery, or traumatic injuries are risk factors [24].

Two of the five cases described in this series presented ON. In one of the patients (case 5), an acute symptomatic episode of secondary ankle synovitis occurred, characterized by pain and limitation, in which other types of pathology were ruled out. In the other case (case 4), we cannot rule out the possibility that it pre-existed CAR-T therapy and that it was simply an incidental finding during the study of the fasciitis. Indeed, patients with hematological disorders have a higher susceptibility for developing ON, including multiple ON (3 or more regions). Several factors have been related to the development of ON in these patients, such as immunosuppressive therapy, cytostatics, and primarily glucocorticoids, and hemostatic and microcirculation changes, among others. Our group described a series of 26 patients with multiple ON, of whom one-fifth had an underlying lymphoproliferative disorder with an average of 5 affected regions [25]. Managing patients with ON, particularly those with multifocal involvement, continues to be a significant challenge for clinicians. Monitoring for the development of new osteonecrotic lesions in high-risk patients and minimizing associated risk factors (such as the use of glucocorticoids) is essential in managing these individuals.

In conclusion, we present a series of rheumatologic complications following CAR-T therapy. One subgroup is characterized by rapidly occurring, localized complications, while another develops inflammatory arthritis later on, with the clinical course and long-term outcomes remaining uncertain.

Clinicians involved in the care and monitoring of CAR-T therapy —primarily intensivists and hematologists— should be aware of these potential complications, along with rheumatologists who will diagnose and manage their progression. As CAR-T therapy becomes more widely used, a clear understanding of the impact and clinical course of these complications will emerge.

Disclosure

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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