Article Title

Mimickers of inflammatory arthritis induced by checkpoint inhibitors.

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· Key Points

-Osteoarthritis and other articular and periarticular mechanical disorders such as myofascial pain, traumatic tendinitis/ tenosynovitis and enthesitis are common in elderly patients. However, they rarely present with significant synovitis.

-Crystal-associated arthritis including gout and pseudogout can be triggered by checkpoint inhibitors and should be ruled out in patients with prior history or other suggestive clinical features.

-Endocrine abnormalities, which can occur as an immune-related adverse event, can cause arthralgia or arthritis.

- Paraneoplastic syndromes are a heterogeneous group of conditions that can include palmar fasciitis and polyarthritis, pancreatitis, panniculitis and polyarthritis, and hypertrophic osteoarthropathy. These conditions can cause joint pain and synovitis.

Synopsis

The differential diagnosis of inflammatory arthritis as an immune-related adverse event can be challenging as patients with cancer can present with musculoskeletal symptoms that can mimic arthritis, because of localized or generalized joint pain. In addition, immune checkpoint inhibitors can exacerbate joint conditions such as crystal-induced arthritis or osteoarthritis, or induce systemic disease that can affect the joints such as sarcoidosis. This distinction is important as the treatment of these conditions can be different from that of immune-related inflammatory arthritis.

Introduction

The development of immunotherapy, and specifically immune checkpoint inhibitors (ICI), has markedly improved the prognosis of patients with various solid tumors. However, ICI can frequently cause immune-related adverse events (irAE), which can be severe. Among these, inflammatory arthritis (irAE-IA) and polymyalgia rheumatica-like (irAE-PMR) can cause severe pain and functional impairment [1]. Patients with irAE-PMR can also present with inflammatory arthritis, so a clear distinction is not always possible[2]. As musculoskeletal symptoms are quite prevalent in the elderly population, patients with cancer who receive ICI may present with musculoskeletal clinical manifestations which may not necessarily be irAE-IA or irAE-PMR. The occurrence of these symptoms may pose a diagnostic and therapeutic challenge for clinicians, especially for oncologists not experienced in the management of rheumatic disease, who must consider alternative causes for their musculoskeletal symptoms including paraneoplastic rheumatic syndromes. The main mimickers of rheumatic syndromes induced by ICI are listed in **Table 1.**

Here, we review some of the main differential diagnoses and mimickers of irAE inflammatory arthritis and PMR in patients with cancer who receive ICI and present with musculoskeletal symptoms. We examine the possible association of some of these presentations with ICI therapy, and which clinical characteristics can be used to differentiate among the various presentations mimicking irAE-IA and irAE-PMR.

Osteoarthritis and mechanical musculoskeletal problems

Development of inflammatory arthritis after ICI initiation needs to be differentiated from mechanically-driven musculoskeletal pathology in order to avoid potentially deleterious treatment with systemic immunosuppressive therapies. Despite these musculoskeletal manifestations not being predominantly inflammatory in character, they can lead to severe pain and disability and consequent ICI discontinuation.

When a patient presents with symptoms of “pain” in and/or around one or more joints, two main characteristics can help narrow the differential diagnoses: (1) intra-articular or extra-articular manifestations and (2) inflammatory versus non-inflammatory presentation.

Arthralgia and myalgia are more common after ICI initiation than is true inflammatory arthritis.

In a multi-center cohort of over 100 patients with rheumatologic and musculoskeletal ICI toxicities, noninflammatory musculoskeletal symptoms comprised almost 15% (18 of 117) of cases [3]. A 2017 systematic review of clinical trial publications reported prevalences of up to 43% for arthralgia and up to 20% for myalgia but only up to 7% of cases with inflammatory arthropathy[4]. In a 2023 retrospective study of over 900 patients treated with ICI for a solid tumor malignancy, almost 10% (9.8%) of patients developed arthralgia or myalgia after ICI whereas only about 4% developed inflammatory rheumatic features [5].

ICI-associated activated osteoarthritis

Clinically, intra-articular noninflammatory pain reflects mechanical and degenerative joint pathology most commonly due to osteoarthritis (OA) or trauma. OA after ICI initiation has been termed ICI-associated activated osteoarthritis (or ICI-aOA) [6,7]. ICI-aOA is characterized by (1) joint pain that is symptomatically worse with activity, improved with rest, and is not associated with significant morning stiffness (i.e., ≤30 min), (2) involvement of a joint or joints characteristically affected by OA, including but not limited to the following: first carpometacarpal (CMCs), distal interphalangeal joints (DIPs), and/or proximal interphalangeal joints (PIPs), knees, hips, cervical, and/or lumbar spine, (3) absence of physical exam findings of inflammation such as swelling, redness, or warmth, and (4) no documented diagnosis of OA preceding ICI initiation.

New symptoms of OA after ICI can be difficult to differentiate from clinical inflammatory arthropathy. As elderly age is a risk factor for both cancer development (and therefore ICI use) as well as OA, ICI-aOA is an important differential diagnosis to consider for patients with “joint pain” after ICI initiation. The largest, multi-institutional case series of ICI-aOA included 36 patients [7]. Of these patients, more than half (19 of 36) had large joint (i.e., hip or knee) involvement and two-thirds had more than one joint affected (24 of 36). Only three had high-grade (>= grade 3) arthropathy while about 40% had grade 2 and 53% met grade 1 criteria [8]. While most cases occurred during ICI therapy, 5 of 36 patients were noted to have ICI-aOA after ICI cessation. In the aforementioned case series, only a few patients had high-grade ICI-aOA that required systemic glucocorticoids (GC) therapy but doses of prednisone ≤20mg were enough for ICI-aOA treatment in all cases [7].

Other Noninflammatory peri-articular ICI toxicities

Symptoms of "joint pain" due to extra-articular non-inflammatory musculoskeletal pathology may comprise a large portion of patients. Extra-articular inflammatory features such as myofasciitis have been associated with ICI-associated inflammatory arthritis, but to date, there is no large study that elucidates how prevalent *non*-inflammatory extra-articular or peri-articular manifestations without arthritis may actually be [9].

Until there are further studies to guide our differential diagnoses in the setting of post-ICI peri-articular pain, various pathologies should be kept in mind for peri-articular pathology leading to symptom of "joint pain" (**Figure 1**). Risk factors for these non-inflammatory markers vary and range from patient's daily activities including sports endeavors and/or daily habits that may contribute to overuse or degeneration.

Metabolic and endocrine-related mimickers of inflammatory arthritis

Metabolic and endocrine disease can resemble or induce various forms of rheumatic complaints, specifically arthralgia or arthritis[10–14].

Crystal-associated arthritis can be found in several forms, most exemplified by gout or calcium pyrophosphate dehydrate (CPPD) deposition (also known as "pseudogout"). The pathophysiology of this disease is based on the deposition of crystals, either monosodium urate (MSU) or CPPD crystals, into joints [13,14]. The inflammatory response in gout can result in various forms, ranging from acute gout attacks to chronic and tophaceus gout, whilst CPPD-afflicted patients have a less flare-like pattern [14].

ICI-associated arthritis can mimic either of these diagnoses after initiation of these medications, as seen in a recent case study [15,16]. The diagnostic evaluation should focus on presence of crystal deposits in either synovial fluid, synovial tissue or even detection via DECT-scans, as these define the specific diagnoses in addition to clinical presentation [17]. In cases where crystal deposits were present without clinical symptoms before ICI-treatment, ICI-induced immune system activation can result in conversion of a previously subclinical response into symptomatic crystalline arthritis. These can even be severely debilitating, as seen in generalized safety assessments of ICI-therapy evaluating arthritis [18,19]. Treatment of the classically characterized crystalline arthritides is focused on crystal substrate removal, pain management, anti-inflammatory medications, and decreasing the production of new crystals, through medications such as colchicine, NSAIDs, GC, and urate-lowering medications (in the case of gout) [20,21].

Potentially ICI-induced symptom treatment follows the same patterns, yet are less well documented as characterization lags and most joint inflammation is only acknowledged as “arthralgia” and/or “arthritis”, even in the most expansive oncological adverse events descriptions [8,18,22,23]. Care should be taken however to distinguish in patients with previous therapies inducing tumor lysis, that can lead to increased uric acid levels and risk of, among other pathologies, gout [24].

Endocrine dysfunction can induce various rheumatic symptoms resembling arthralgia or arthritis as a result of the primary pathology [11]. The most common is hypothyroidism that occurs in 5% of the population and may even primarily present with musculoskeletal symptoms [11]. These musculoskeletal symptoms can present as symmetrical arthropathy, carpal tunnel syndrome, (poly)myalgia or even generalized muscle weakness [11] . Hypoparathyroidism can simulate arthralgia via increase of free calcium within a patient, as this can lead to increased joint calcification, usually subclinical, but also to renal disease [11]. Adrenal insufficiency has also been indicated as a potential cause of arthralgic complaints, but these are less the result of inflammatory activity and more a generalized decrease of muscle strength and loss of conditioning due to a decrease in cortisol levels [25]. Finally, hypophysitis or pituitary dysfunction can indirectly cause all of the abovementioned symptoms due to its role in the endocrine regulation via production and distribution of stimulating hormones [26]. All of the abovementioned endocrine dysfunctions are potential adverse events of ICI-therapy due to auto-immune inflammation of the endocrine tissue, with an expected incidence of 5% up to 40% depending on the study and specific ICI-therapy [27–29].The differentiation between actual inflammatory arthritis and arthritis due to endocrine dysfunction depends on proper patient examination and diagnostic evaluation of the various hormonal axes.

Unfortunately, at time of diagnosis many endocrinopathies are already irreversible and require hormone replacement therapy [29]. Once these endocrinopathies are properly treated or replacement therapy has been titrated, most of the arthralgic symptoms also disappear if there was no permanent change or damage [29].

The incidence of diabetes mellitus (DM), most commonly type 2 (96%, characterized by insulin resistance), has increased enormously in recent years [30]. That increase has grave implications for musculoskeletal health, as DM is associated with several forms of arthropathy [10]. Most often this presents in the form of tendinopathy or arthropathy in a specific limb caused a combination of neurological, joint and skin dysfunction that can be severely debilitating and may ultimately lead to

amputation of the affected extremity, with an extreme case being Charcot's arthropathy (CA) [10,29,31]. Other arthralgic complaints known to occur more frequently in patients with DM are OA, diabetic hand syndromes including flexor tenosynovitis ("trigger finger"), diabetic cheiroarthropathy ("stiff hand syndrome"), Dupuytren's contracture, and adhesive capsulitis ("frozen shoulder)[32–34]Diabetic arthropathy due to ICI-therapy also occurs via this pathology, with the difference that ICI-induced DM is most likely to be similar to type 1 diabetes (characterized by insufficient insulin production) [29,35]. This is due to the fact that in the insulin producing pancreatic islets, PD-1 and PD-L1 interaction occurs, which can result in auto-reactivity once ICI-therapy is used [36]. The arthropathies resulting from DM, whether ICI-related or not, can also be treated by anti-inflammatory treatment, but can require surgical and antibiotic treatment in the case of CA [10,29,31].

Sarcoidosis

Sarcoidosis is a granulomatous disorder that can involve almost any organ [37]. The most common presentation is in the lungs with bilateral hilar lymphadenopathy and parenchymal involvement with a nodular or reticular pattern. The disease is often diagnosed incidentally in asymptomatic patients following imaging of the chest for an unrelated reason.

The prevalence of sarcoidosis is slightly under 1 in 1000, with variations across countries [38]. In the United States it is most common in African Americans, more frequent in women, and typically diagnosed between the ages of 30 and 60. Histopathology typically shows non-necrotizing granulomas with macrophages, multinucleated giant cells and CD4 positive T lymphocytes. The etiology of sarcoidosis remains elusive, despite advances in understanding the immunopathogenesis of the disease. There is clearly an inflammatory and immune process that leads to the development of the granulomas, but although there is support for an initial infectious trigger, no unique or consistent infectious antigens have been identified [39].

The clinical features of sarcoidosis vary according to the location of the sarcoid granulomas, which can affect a variety of organs. While isolated pulmonary sarcoidosis is often asymptomatic, involvement in other organs is generally diagnosed because of related clinical manifestations and symptoms leading to testing and biopsy of the affected sites. Musculoskeletal and rheumatic manifestations of sarcoidosis are common in symptomatic patients and can include bone involvement, sarcoid arthropathy, myopathy, vasculitis, and sicca syndrome [40]. Sarcoid arthritis can develop in up to 15% of patients [41]. Acute arthritis is often a manifestation of Löfgren syndrome, an acute presentation of sarcoidosis with hilar

adenopathy, erythema nodosum, fever and arthritis. The most common pattern of arthritis is symmetrical oligoarthritis of the lower extremities, especially ankles and knees. Chronic persistent arthritis is rare, and can present with granulomatous synovitis, or joint swelling adjacent to a sarcoid lesion in the bone.

Development of *de novo* sarcoidosis has been reported in patients receiving ICI [42]. The interval between onset of therapy and development of symptoms can range from one month to two years. Most patients are symptomatic and present with pulmonary involvement and subcutaneous nodules. In most cases the disease is self-limited, and patients can continue ICI therapy. Flares of sarcoidosis can also occur in patients with a pre-existing history of the disease [43]. Nonetheless, most patients with a remote history of sarcoidosis do not experience flares when receiving immunotherapy.

As sarcoidosis can present with acute arthritis, it is important to distinguish this entity from irAE-IA occurring on its own, as the pathogenesis, course, and response to treatment of both disorders might differ. Patients with ICI-induced sarcoidosis invariably have mediastinal lymph nodes, as well as involvement of other organs such as the skin, or the eyes.

Paraneoplastic syndromes

Palmar fasciitis and polyarthritis syndrome (PFPAS)

PFPAS is characterized by a sudden onset pain in hands and/or feet accompanied by marked stiffness and progressive thickening of the palmar/plantar fascia with contractures similar to Dupuytren´s contracture. Occasionally, severe progressive fibrosis leads to fibrosis of palmar surfaces with a "wooden feeling" with a deepening of the palmar crease causing a 'groove sign' (**Figure 2**).

Polyarthritis usually is symmetric and involves CMCs, PIPs and occasionally wrists. Shoulder pain when present is characterized by limitation of range of motion and can present in the form of adhesive capsulitis [44,45]

PFPAS is a rare paraneoplastic syndrome affecting predominantly female patients and has been reported mainly for ovarian, breast, and other female reproductive organ cancers. Other less common carcinomas include lung, gastrointestinal, pancreas and, on some occasions, hematological neoplasms. According to the biggest systematic review of patients with PFPAS [45], in more than 70% of patients, PFPAS symptoms preceded the diagnosis of underlying cancer. Few cases of PFPAS related to non-

malignant conditions have been reported, mainly ovarian benign cysts [46]. To the best of our knowledge, there are no previous reports of PFPAS induced by ICI.

Laboratory markers are not specific for the diagnosis of PFPAS. Erythrocyte sedimentation rate and C-reactive protein could be elevated but not in all cases. Rheumatoid factor and antinuclear antibodies (ANA) are negative as well as ANA subtype specificities. Assessment of serum tumor markers such as CA125 can help identify the underlying malignancy for those cases without an established diagnosis.

Symptomatic treatment of PFPAS is based on NSAIDs and oral GC with some disappointing results according to the stage of fibrosis. Experience with disease-modifying anti-rheumatic drugs (DMARD) is anecdotal with mixed results. Improvement of polyarthritis often occurs after successful treatment of the ovarian or other underlying carcinoma[45] .

Pancreatitis, panniculitis, and polyarthritis syndrome

The pancreatitis, panniculitis, and polyarthritis (PPP) syndrome is characterized by the symptom triad of skin and joint involvement that accompanies benign or malignant pancreatic disease in 2-3% of cases [47–50]. The skin lesions caused by lobular panniculitis can closely resemble erythema nodosum with erythematous livid subcutaneous nodules that are predominantly symmetrical on the lower limbs. Tenderness can be absent; however, the main difference is a lipolysis-driven spontaneous brown discharge. Histopathology shows typical focal fat necrosis and the presence of “ghost-like” adipocytes without nuclei due to pancreatic enzyme digestion [48–51].

Skin manifestations can be the sole symptom of pancreatic disease (so called pancreatic panniculitis (PP)). Additional joint involvement in PPP is mostly polyarticular, typically affecting the ankles, followed by knees and hands, with acute sarcoidosis, Behçet disease and polyarteritis nodosa as frequent differential diagnoses particularly in the absence of abdominal symptoms. Both in skin lesions and synovial fluid, high lipase concentrations have been previously reported, demonstrating the pathophysiological role of the pancreatic disease in the PPP syndrome [47–49,51,52].

In previous large systematic literature reviews on PP/ PPP syndromes (any cause: [47,48], n=131 and 148 (including PP-cases, malignancies in 20 and an unreported number of PPP cases); [49], n=59 (7 malignancies);[52], n=84 (34 malignancies): PPP affected mainly males (~75%) of age 50-55 years with nearly 2/3 developing skin lesions ahead of the diagnosis of pancreatic disease. The delay is attributable to the absence of abdominal symptoms in approximately half of the PPP patients [49], however, lipase and/or amylase were elevated in 147/148 patients as helpful indicator [47]. The proportion of neoplastic

causes varied between 12-44% of PPP-cases [47–49,52]with acinar cell carcinoma as the leading cause, although it accounts for only approximately 1-2% of all pancreatic neoplasms [47,53].

Eosinophilic fasciitis

Eosinophilic fasciitis (EF) is a rare inflammatory disorder of the subcutaneous fascia and skin, originally defined as “diffuse fasciitis with eosinophilia” by Shulman in 1974, and later named “eosinophilic fasciitis” by Rodnan in 1975 [54]. The diagnosis is based on several factors, including the clinical presentation characterized by skin induration, laboratory findings including elevated eosinophil levels and increased markers of inflammation, characteristic changes seen on magnetic resonance imaging (MRI) scans, and distinctive histopathological findings. It typically presents initially with non-pitting oedema on the full circumference of the forearms and/or lower legs, and is usually symmetric (excluding hands and feet). Later in the course of the disease, symmetrical induration ("peau d'orange") and characteristic retraction of the skin around the cutaneous veins (groove sign) occur (**Figure 3A**). Although in the initial edematous phase the skin changes may resemble early sclerodermatous changes, the more advanced skin (as opposed to the smooth, shiny skin surface of scleroderma) has a unique irregular, woody "peau d'orange" texture, which is most common on the extremities, neck and trunk.

The main findings on MRI of EF often include thickening and enhancement of the fascial layers, indicating inflammation and involvement of deep soft tissues (**Figure 3B**). Abnormalities are typically limited to the fasciae, sparing muscles and hypodermic fat [55]. Muscle biopsy usually shows thickening of the fascia, fibrin deposits, and inflammatory infiltrates comprised of mainly CD8 + lymphocytes (CD4/CD8 ratio < 1) and eosinophils. It is important to note that eosinophils or major basic eosinophilic proteins are not always present in affected tissues [56] **(Figure 4)**.

According to recently published criteria, the classification of EF requires the presence of the major criterion symmetric plate-like sclerotic lesions present on the four limbs, and at least one of two minor criteria: 1) Histology of a skin/ fascia biopsy showing fibrosis with thickening of the fascia and cellular infiltration of eosinophils and monocytes, or 2) Thickening of the fascia seen on imaging studies, usually MRI [57]. Arthritis has been reported in up to 40% of the patients, more commonly affecting joints in the areas adjacent to fasciitis [58].

In the context of malignancies, EF has been described as a paraneoplastic phenomenon and as an irAE. In paraneoplastic EF, concomitant hematological malignancies (e.g. aplastic anemia, multiple myeloma, myeloproliferative syndromes, myelodysplastic syndromes, lymphoma) and solid tumors (e.g. prostate,

bronchial and breast cancer) have been reported in 65 % and 35 % of the patients, respectively [59]. ICI-induced EF appears to be more associated with PD-1/PD-L1 inhibition rather than CTLA-4 inhibition [60].

As data on the management of malignancy-associated EF are limited, the standard therapy for EF is applied with the use of GC, in combination with methotrexate in resistant cases. For irAE EF, holding ICI therapy can be considered, and for paraneoplastic EF, efficient treatment of the underlying disease appears to be beneficial [60].

Hypertrophic osteoarthropathy

Hypertrophic osteoarthropathy (HOA) is a rare syndrome that is characterized by abnormal proliferation of the skin and periosteal tissues that manifests as digital clubbing, periostitis of the long (tubular) bones (**Figure 5**) and, in some cases, arthritis. It can be referred to as pachydermoperiostosis when considered a primary condition (hereditary or idiopathic), however in ~80% of cases, HOA is a secondary condition associated with an underlying pulmonary, cardiac, hepatic or intestinal disease, or as a paraneoplastic syndrome, most commonly due to intrathoracic neoplasms [61]. HOA represents an important irAE mimicker as it can lead to both joint and bone pain that may become clinically apparent prior to or following ICI therapy, but may not necessarily require treatment with immunosuppression because it is driven by the underlying cancer itself [62,63].

Secondary HOA is typically associated with underlying pulmonary disease, with bronchogenic carcinoma being the most frequent association where it is observed in up to 17% of patients [64]. Growth factors, such as platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF), and other cytokines are thought to be major contributors to HOA pathogenesis [65].

HOA leading to periostosis can be asymptomatic or, in more severe cases, may lead to a deep burning pain in the distal extremities that causes dysesthesia. There may be accompanying sweating, clumsiness, and stiffness of the hands [66]. Joint symptoms from HOA range from mild to severe arthralgias, most typically involving metacarpal joints, elbows, knees and ankles. Diminution in range of motion may be observed, with contractures in severe cases. Joint pain is typically caused by periosteal inflammation such that symptoms improve when periostitis is halted [67].

The diagnosis of HOA can be made based on physical exam findings of finger clubbing, and radiographically based on the findings of periostitis and symmetrical thickening of distal tubular bones (tibia, fibula, radius, ulna). Plain radiographs can show bone formation with hypertrophy and bone dissolution with acro-osteolysis (seen in distal tufts of patients who have longstanding HOA) [68].Technetium (Tc) 99m radionuclide bone scans, the most sensitive diagnostic modality to detect and evaluate the extent of HOA, show increased uptake of the tracer in periosteum [69].

There are two case reports of HOA improving with the use of ICI. Johns et al. report a case of HOA causing bilateral severe knee pain in the context of T3N2 Stage IIIB non-small cell lung cancer [62]. The patient was treated with neoadjuvant chemotherapy (carboplatin and pemetrexed), followed by chemo-immunotherapy with carboplatin, pemetrexed and pembrolizumab. She then underwent chemo-radiation with concurrent carboplatin and paclitaxel. Her knee pain from HOA improved substantially and she remained asymptomatic while undergoing durvalumab consolidation. Another similar case showed prompt resolution of HOA with the successful use of pembrolizumab, carboplatin and pemetrexed chemoimmunotherapy [70].

Other rare disorders

-POEMS syndrome

POEMS (Polyneuropathy, Organomegaly. Endocrinopathy, Monoclonal plasma cell disorder, Skin changes) syndrome is a rare disorder characterize by plasma cell dyscrasia, accompanied by varying multiorgan systemic manifestations [71]. There are two mandatory criteria for the diagnosis of POEMS, polyradiculoneuropathy, and evidence of a monoclonal plasma cell disorder in serum and/or urine [72]. Other diagnostic criteria include osteosclerotic bone lesions, elevated VEGF levels, evidence of Castleman disease (major criteria,) organomegaly, endocrine abnormalities, skin changes, extravascular volume overload, thrombocytosis/polycythemia, and papilledema (minor criteria) [73].

POEMS is a very rare disorder, presenting in the 5th or 6th decade of life, and is slightly more prevalent in males compared to females. The etiology of POEMS is unknown, but the disease is characterized by release of pro-inflammatory cytokines, and marked production of VEGF which results in increased vascular permeability, and related clinical manifestations. [74]. POEMS can be considered as a paraneoplastic syndrome in response to the development of a plasma cell neoplasm. No clear association with solid tumors has been established, although there is a case report of POEMS presenting synchronously with breast cancer [75].

The onset of the disease is generally insidious and, by definition, all patients present with neurologic symptoms, initially sensory, with possible motor involvement at a later stage. About two-thirds of the patients have hormonal abnormalities including hypothyroidism, adrenal insufficiency, and hypogonadism as the most frequent endocrine manifestations. Organomegaly including hepato-splenomegaly and lymphadenopathy is common. Patients may present with a variety of skin changes

such as hyperpigmentation, hemangioma, Raynaud's phenomenon, sclerodermatous changes, flushing and nail changes. Patients have extravascular volume overload resulting in peripheral edema, and occasionally can develop ascites or pleuritis. Multicentric Castleman disease, a non-clonal lymphoproliferative disorder with an overproduction of interleukin 6 (IL-6), can be associated with POEMS [76].

While there are no descriptions of POEMS after administration of ICI, some of the manifestations of this syndrome can overlap with the clinical presentation of irAEs especially when affecting various organs, causing endocrine abnormalities, skin changes and other manifestations. Lower extremity swelling in conjunction with pain could be misdiagnosed as arthritis. The diagnosis of POEMS is based on the clinical presentation and the detection of a monoclonal immunoglobulin, typically a lambda light chain, in serum or urine. An increased serum VEGF can also aid in the diagnosis [71].

Sweet syndrome

Sweet syndrome is an acute febrile neutrophilic dermatosis that can be accompanied by extracutaneous manifestations, first described in 1964 by Richard D. Sweet [77]. As it can present with musculoskeletal manifestations (joint, muscle, and bone) in between 12-56% of patients [78] it is important to be aware of Sweet syndrome as one of the mimickers of rheumatic irAEs. Sweet syndrome can be observed in 3 different clinical contexts: 1) classical Sweet syndrome, which can be associated with infections, inflammatory bowel disease, and less commonly with other autoimmune diseases such as rheumatoid arthritis, sarcoidosis, Behçet's, relapsing polychondritis, and VEXAS [79], malignancy-associated Sweet syndrome, more strongly associated with hematologic malignancies (acute myeloid leukemia in particular, as well as other myeloproliferative disorders) but occasionally with solid tumors [78,80], and 3) drug-induced Sweet syndrome, most commonly observed following granulocyte colony stimulating factor (G-CSF) administration and other medications [81], but also rarely reported as an irAE with ICI.

Sweet syndrome is characterized by the sudden onset of tender papules, plaques, or nodules comprised of a diffuse infiltrate of predominantly neutrophils in the upper dermis. Sweet syndrome can often be accompanied by fever and arthralgias. In adults, there is a slight female predilection [79]. The pathogenesis of Sweet syndrome is thought to involve cytokines that promote neutrophil activation and infiltration, and the occurrence of Sweet syndrome following G-CSF treatment supports this mechanism [81].

The two major diagnostic criteria for Sweet syndrome include 1) the abrupt onset of painful erythematous plaques or nodules and 2) histopathology showing a dense neutrophilic infiltrate without

evidence of leukocytoclastic vasculitis. Minor diagnostic criteria (need 2 out of 4) include 1) fever > 38^{o}C, 2) association with an underlying hematologic or visceral malignancy, inflammatory disease or pregnancy, or preceded by an infection (upper respiratory or gastrointestinal), 3) abnormal laboratory values: ESR > 20 mm/hr, elevated C-reactive protein, leukocytes > 8000, or neutrophils > 70% (need 3 out of 4), and 4) demonstration of an excellent response to treatment with systemic GC or potassium iodide [82].

Sweet syndrome as an irAE is relatively rare. Five case reports have described metastatic melanoma patients who developed Sweet syndrome in response to ipilimumab (anti-CTLA4) monotherapy [83], and one case report described Sweet syndrome occurring with pembrolizumab monotherapy [84]. The median time to onset was 8.9 weeks (with a range of 6-12 weeks) after first administration of the ICI. Resolution of Sweet syndrome was achieved in all cases with oral or intravenous GC administration, and one patient received dapsone simultaneously, without recurrence of symptoms. In three of the five cases, ICI therapy was permanently discontinued and in one case, switch to nivolumab monotherapy was employed [83,85,86]. The occurrence of musculoskeletal involvement with Sweet syndrome has been reported in 12-56% of classical Sweet syndrome cases, 26% of cases associated with hematologic malignancies, 34% of cases associated with solid tumor malignancies, and 21% with drug-induced Sweet syndrome [79]. In addition to articular findings (acute sterile arthritis, arthralgias), extracutaneous manifestations of Sweet syndrome can include bone findings (focal aseptic osteitis, pigmented villonodular synovitis, sterile osteomyelitis), and muscle findings (myositis, fasciitis, myalgias, tendonitis, and tenosynovitis) [79].

Erythromelalgia

Erythromelalgia is a rare clinical syndrome characterized by intermittent hyperperfused, red, hot, painful skin and is three times more in women. It predominantly affects the skin of the feet (~ 90%) but may also (concomitantly) affect the upper extremities, particularly the hands (up to 30%) [87]. Atypical, very rare manifestations include typical manifestations skin areas of neck, ears, cheeks, genitals. Patients often tend to cool their skin to experience some relief.

Erythromelalgia has been associated with myeloproliferative disorders (< 10 % of cases) and less commonly with other cancers, connective tissue disease and infections [88]. When present, treatment consists of managing the underlying disease. Treatment, although based very limited and efficacy, typically involves a combination of non-pharmacological interventions (e.g.

avoidance of triggering factors such as ambient heat and cooling measures for short exposure time) and pharmacological therapy using topical treatment with lidocaine-patches compounded amitriptyline 2 %/ketamine 0.5 % gel, and compounded midodrine 0.2 % cream [87]

Summary

The clinical approach to musculoskeletal pain in patients with cancer under ICI therapy requires a comprehensive assessment due to the multifactorial nature of articular and peri-articular pain in this population. Firstly, a detailed medical history should be obtained, focusing on the onset, duration, and characteristics of the pain, with emphasis of inflammatory pain and arthritis. A thorough physical examination is crucial to identify the precise location of pain, assess joint mobility, muscle strength, and functional limitations. Special attention should be given to ruling out red flags or signs of serious underlying neoplasm. Additionally, considering the high prevalence of comorbidities in the elderly, including crystal-associated arthritis, metabolic and endocrinologic diseases and diabetes, it is vital to evaluate the patient's overall health status. Identification of inflammatory processes susceptible to treatment with immunosuppressive agents is vital in crucial to avoid potentially deleterious treatment of immunosuppressive drugs. This is even more significant in the context of ICI therapy where unnecessary systemic immunosuppression may abrogate ICI efficacy.

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Table 1. Mimickers of rheumatic and systemic syndromes induced by ICI

Inflammatory disorders

- Crystalline arthritis (gout or pseudogout)
- Paraneoplastic arthritis
  - Palmar fasciitis and polyarthritis syndrome
  - Remitting seronegative symmetrical synovitis with pitting edema (RS3PE)
  - Pancreatic panniculitis with polyarthritis
- Sarcoid arthropathy

Mechanical/degenerative musculoskeletal disorders

- Osteoarthritis/ activated osteoarthritis
- Rotator cuff tendinitis
- Traumatic tendinitis/ tenosynovitis
- Mechanically induced enthesitis

Other chronic pain disorders

- Fibromyalgia
- Complex regional pain syndrome

Infectious diseases

- Post-viral arthritis/arthralgia (e.g., HBV, HCV, HIV, parvovirus B19, SARS-CoV-2)
- Bacterial arthritis
- Mycobacterial arthritis
- Lyme arthritis

Metabolic and bone diseases

- Tumor-induced osteomalacia
- Metastasis (in proximity to joints)
- Hypertrophic osteoarthropathy (Marie-Bamberger disease)

Neuropathies

- Chemotherapy induced neuropathy
- Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes syndrome (POEMS syndrome)
- Parsonage Turner syndrome

Endocrinologic

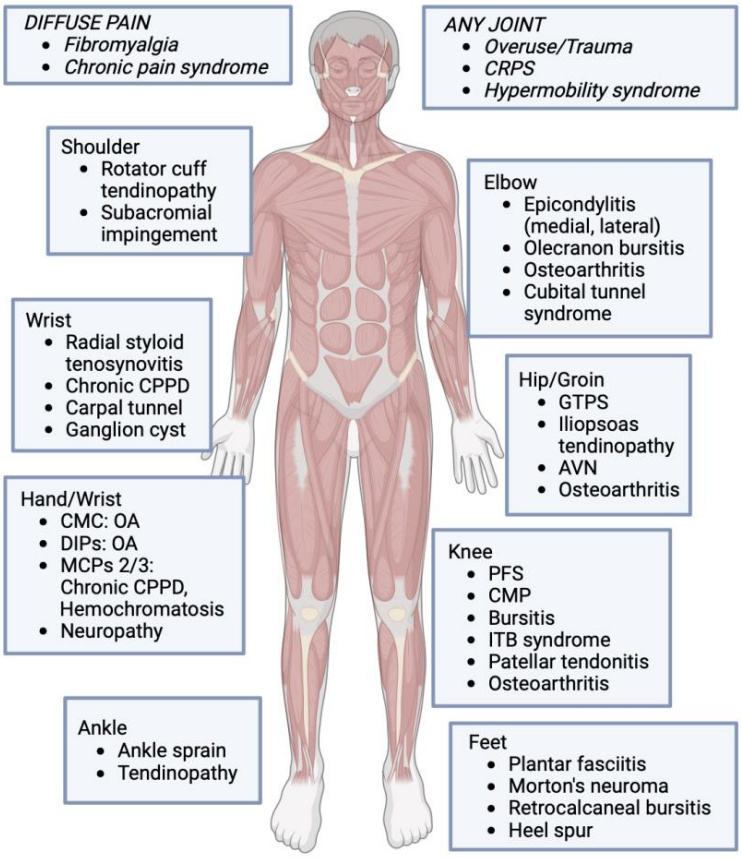
- Arthralgia associated to endocrine disease (e.g., hypothyroidism)
- Hypophysitis

Cutaneous syndromes

- Eosinophilic fasciitis
- Paraneoplastic vasculitis
- Sweet syndrome
- Erythromelalgia

Fig 1. Non inflammatory periarticular diagnoses after ICI initiation

Pain resulting from issues of structures *around the* joint instead of within the joint can be described by patients as "joint pain." This figure reflects peri-articular pathologies that are predominantly non-inflammatory in character to consider when patient reports symptoms of "joint pain."



AVN: Avascular necrosis, CMP: Chondromalacia patella, CPPD: Calcium pyrophosphate disease,
CRPS: Chronic regional pain syndrome; GTPS: Greater trochanter pain syndrome,
PFS: Patellofemoral syndrome

Fig 2. **A.** Palmar fasciitis with palmar erythema and visible flexion contracture in second and third fingers and left palmar surface with deepening of the palmar crease causing a ‘groove sign’. **B.** Lateral view showing disabling flexion contracture of her fifth finger in right hand.

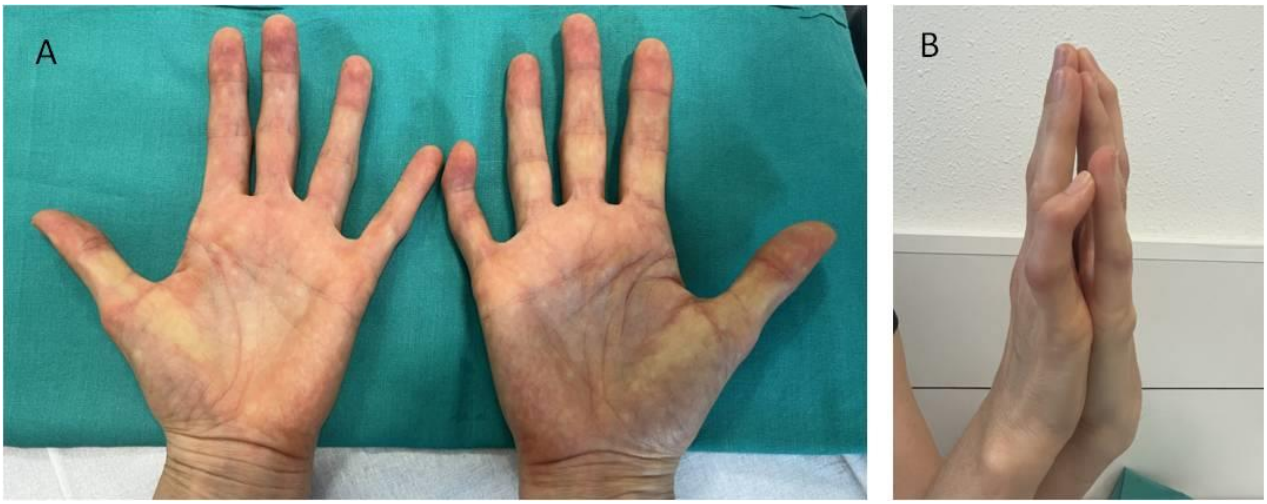


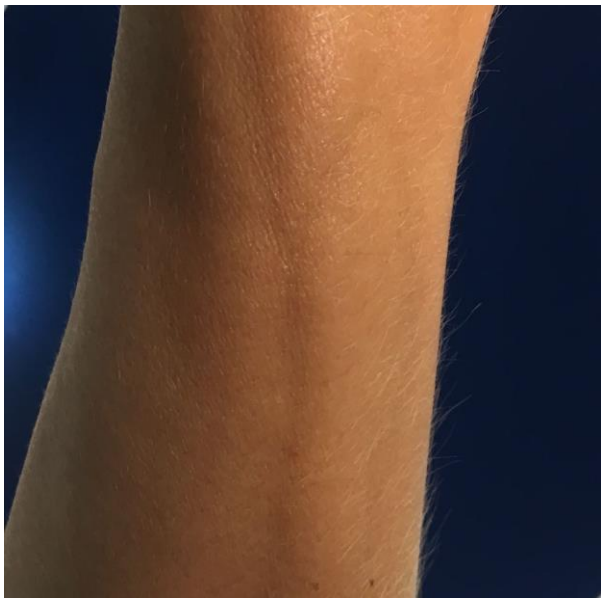
Fig 3. Eosinophilic fasciitis

A. Linear depressions (groove sign) on the right forearm

B. Axial STIR MRI: Abnormal signal intensity and enhancement is observed in almost all fascia, with greater intensity in the deltoid (stars), vastus lateralis (arrows), and calf muscles (triangle).

(Courtesy of Dr. José C. Milisenda, From Internal Medicine Department, Hospital Clínic, Barcelona)

A



B

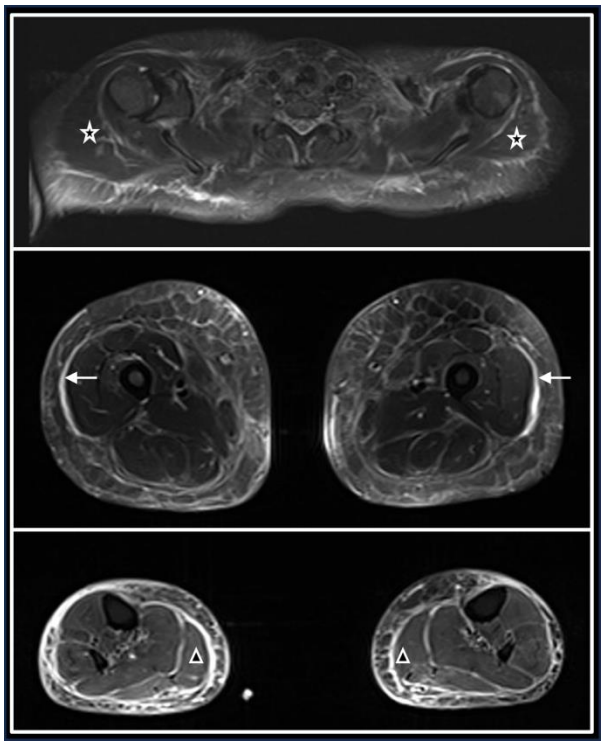


Fig 4. Histopathology of eosinophilic fasciitis

Cross-sections of frozen muscle. A and B, H&E staining of muscle and fascia, showing perivascular inflammatory infiltrates (stars). C and D, immunohistochemistry for MHC-I and MHC-II, showing universal positivity for both techniques, both at the perimyseal and muscular levels.

(Courtesy of Dr. José C. Milisenda, From Internal Medicine Department, Hospital Clínic, Barcelona)

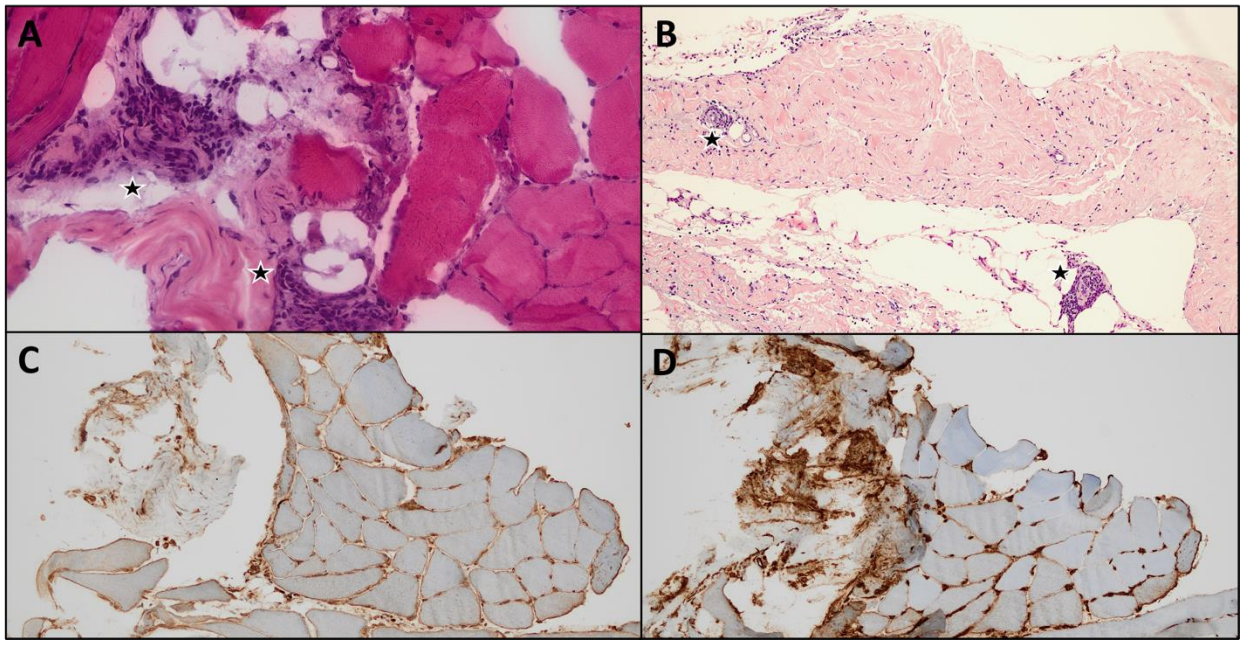


Fig 5. Hypertrophic osteoarthropathy
A. Feet with digital clubbing predominantly in second and third fingers
B. Simple X-rays of the ankles showed a lamellar type of periosteal reaction