Autoimmune Complications of Immune Checkpoint Inhibitors for Cancer

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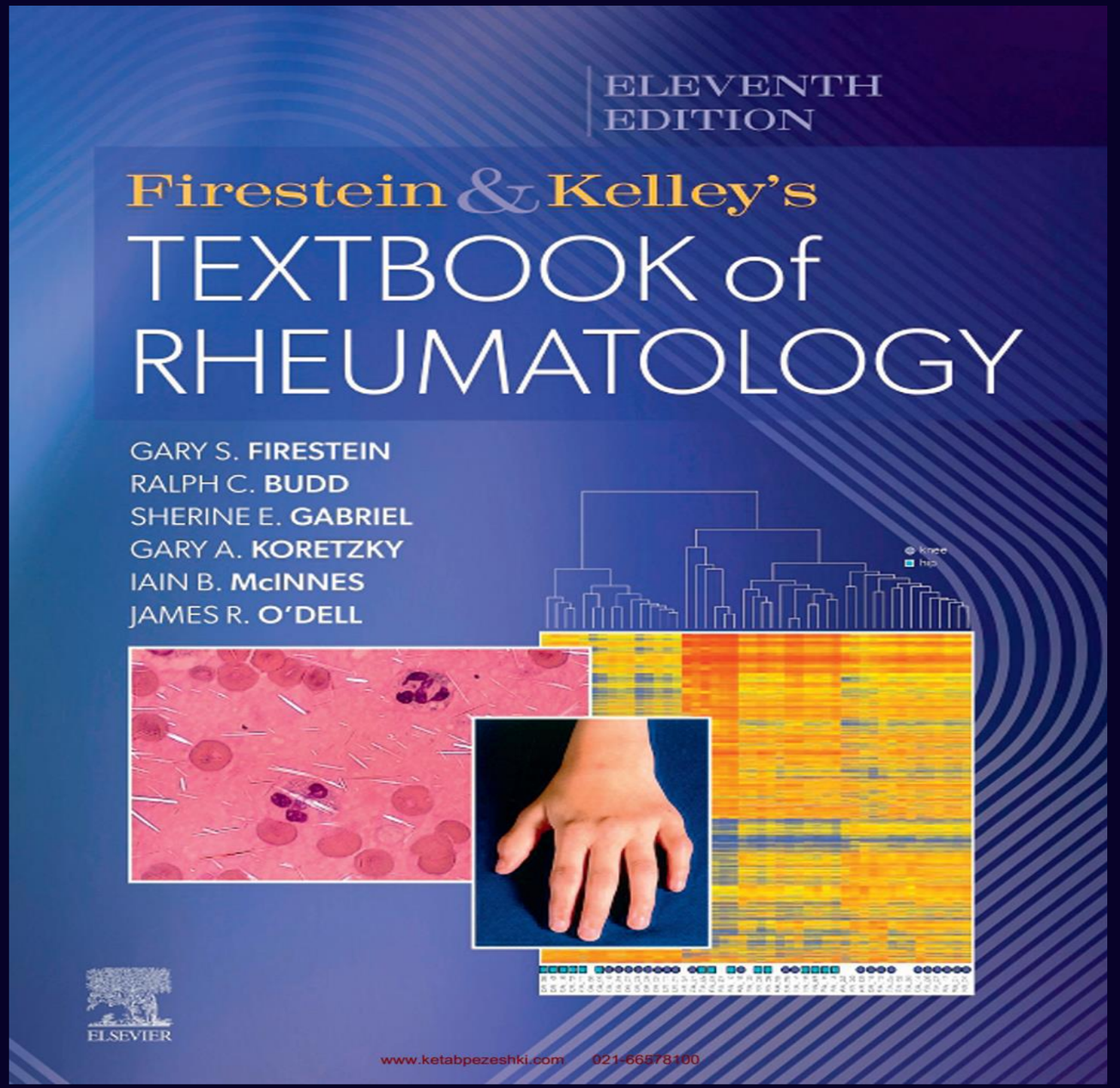
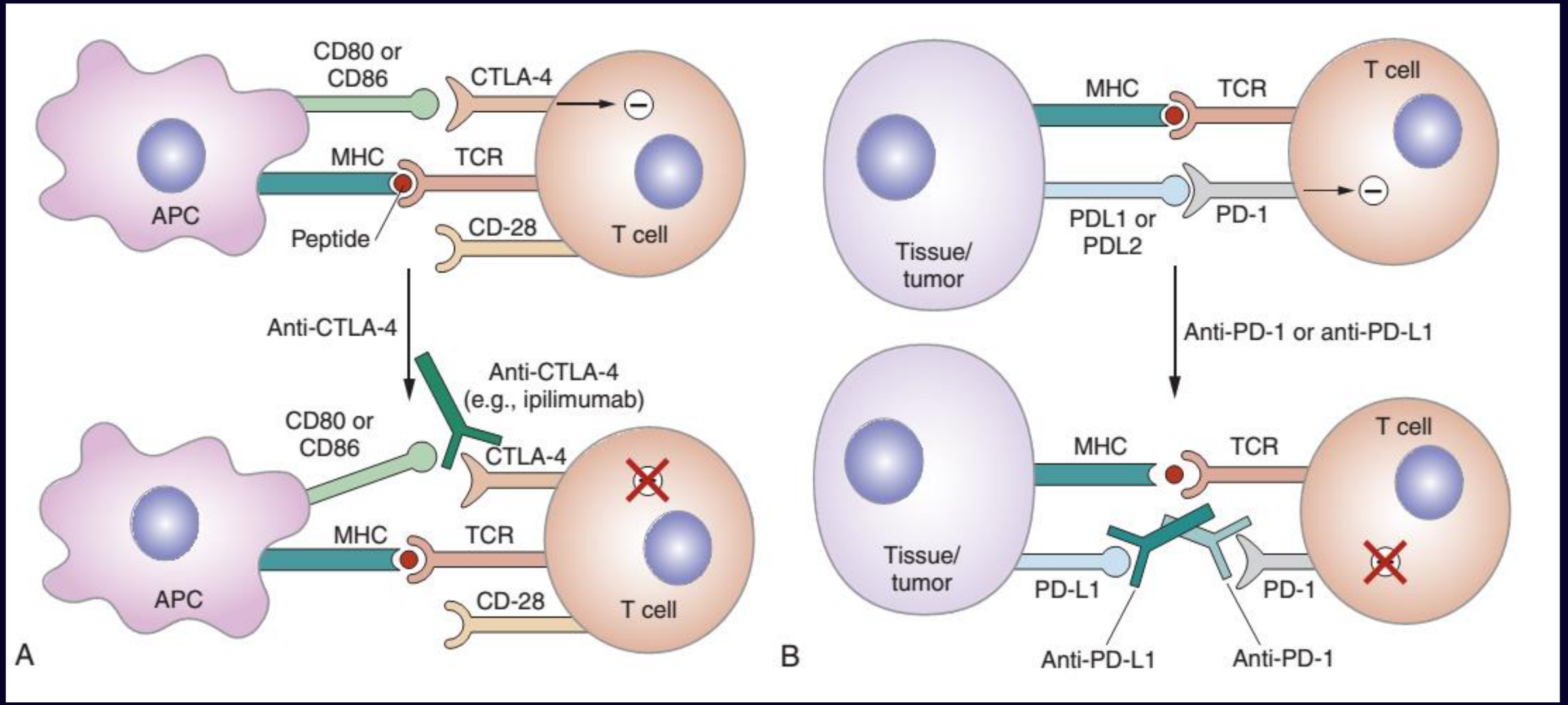


introduction

- Immune checkpoint inhibitors, used for the treatment of cancer, can cause a wide variety of inflammatory syndromes known as **immune related adverse events (irAEs)** including those with rheumatic phenotypes.



Immune Checkpoint Inhibitor Mechanism of Action

Drug/s	Target	Year First Approved (FDA)	Indication(s)
Ipilimumab	CTLA-4	2011	Melanoma
Nivolumab	PD-1	2014	Melanoma, NSCLC, RCC, refractory Hodgkin's lymphoma, urothelial carcinoma, SCCHN
Pembrolizumab	PD-1	2014	Melanoma, NSCLC, urothelial carcinoma, MSI-H solid tumors, SCCHN, HCC
Atezolizumab	PD-L1	2016	Urothelial carcinoma, NSCLC
Avelumab	PD-L1	2017	Merkel cell carcinoma, urothelial carcinoma
Durvalumab	PD-L1	2017	Urothelial carcinoma, NSCLC
Cemipilab	PD-1	2018	Advanced cutaneous squamous cell carcinoma
Ipilimumab/ Nivolumab	CTLA-4 and PD-1	2015	Melanoma, renal cell carcinoma

ICIs With Targets and FDA-Approved Indications

Immune-Related Adverse Events (irAEs)

- ✓ Systemic Adverse Events
- ✓ Dermatologic Adverse Events
- ✓ diarrhea/colitis
- ✓ Hepatotoxicity
- ✓ endocrinopathies
- ✓ pneumonitis

➢ **Less common :**

- ✓ Rheumatologic Adverse Events
- ✓ Neurologic Adverse Events
- ✓ Cardiovascular toxicity
- ✓ Hematologic
- ✓ Exocrine pancreas
- ✓ Eye
- ✓ Kidney

Immune-Related Adverse Events (irAEs)

➢ There is significant heterogeneity in :

- prevalence
- Severity
- Time of onset
- relationship to type of ICI
- relationship to underlying tumor type

irAEs

➢ Prevalence :

➢ the **most common** irAEs are **dermatologic** conditions and **hypothyroidism**.

- **Rare** but potentially severe irAEs include **myocarditis**, occurring in less than 1% of patients with irAEs, and **neurotoxicities** such as Guillain-Barré syndrome, encephalitis, and myasthenia gravis.

➢ Severity :

- both **pneumonitis** and **colitis** can be life threatening in some cases but can also be mild and self-limited. **rash** may respond to topical therapy or can be severe

irAEs

- **Time of onset** : Some irAEs, such as colitis and rash, tend to develop early in the treatment course, while others, like pneumonitis and inflammatory arthritis, have a variable time to onset.

- **type of ICI :** Colitis and hypophysitis are more common with CTLA-4 inhibition. Pneumonitis, hypothyroidism, and vitiligo, are more common with PD-1 inhibition.

- **underlying tumor type:** Patients with melanoma are more likely to have dermatologic and gastrointestinal irAEs but less likely to have pneumonitis

irAEs

➢ **Grading :**

- 1-mild
- 2-moderate
- 3-severe
- 4-life threatening

Potential Mechanisms Underlying irAEs

- Cytokine-mediated inflammatory damage
- Expression of CTLA-4 or PD-1/PD-L1 on target tissue
- Shared antigen recognition by T cells
- Activation of pre-existing subclinical autoimmunity
- Perturbations of the microbiome

Immune-Related Adverse Events (irAEs)

➢ SYSTEMIC ADVERSE EVENTS

- **Fatigue :**

✓ Fatigue is among the most common side effects (16 to 24 percent for the anti-PD-1 and anti- PD-L1 agents and approximately 40 percent in those treated with ipilimumab)

✓ generally mild

✓ exclude endocrine disorders

- **Infusion-related reactions**

Immune-Related Adverse Events (irAEs)

➢ DERMATOLOGIC AND MUCOSAL TOXICITY

- **most common** irAE : Approximately 50 percent of patients treated with ipilimumab will experience rash and/or pruritus, and approximately 30 to 40 percent of those treated with nivolumab or pembrolizumab
- **earliest** irAE (3.6 weeks after treatment initiation)
- reticular, maculopapular, faintly erythematous rash
- Vitiligo : commonly
- Alopecia
- Oral mucositis and/or complaints of dry mouth : anti PD-1
- topical glucocorticoid creams,oral antipruritics, oral or IV glucocorticoid

Immune-Related Adverse Events (irAEs)

➢ DIARRHEA/COLITIS

- a common clinical complaint / six weeks into treatment
- differential diagnosis ?
- diarrhea is much higher in patients receiving **CTLA-4 -blocking** antibodies

➢ HEPATOTOXICITY

- Elevations in serum levels of the hepatic enzymes,
- Most episodes : asymptomatic
- time of onset is 8 to 12 weeks after initiation of treatment

Immune-Related Adverse Events (irAEs)

- **Endocrinopathies :** nonspecific symptoms

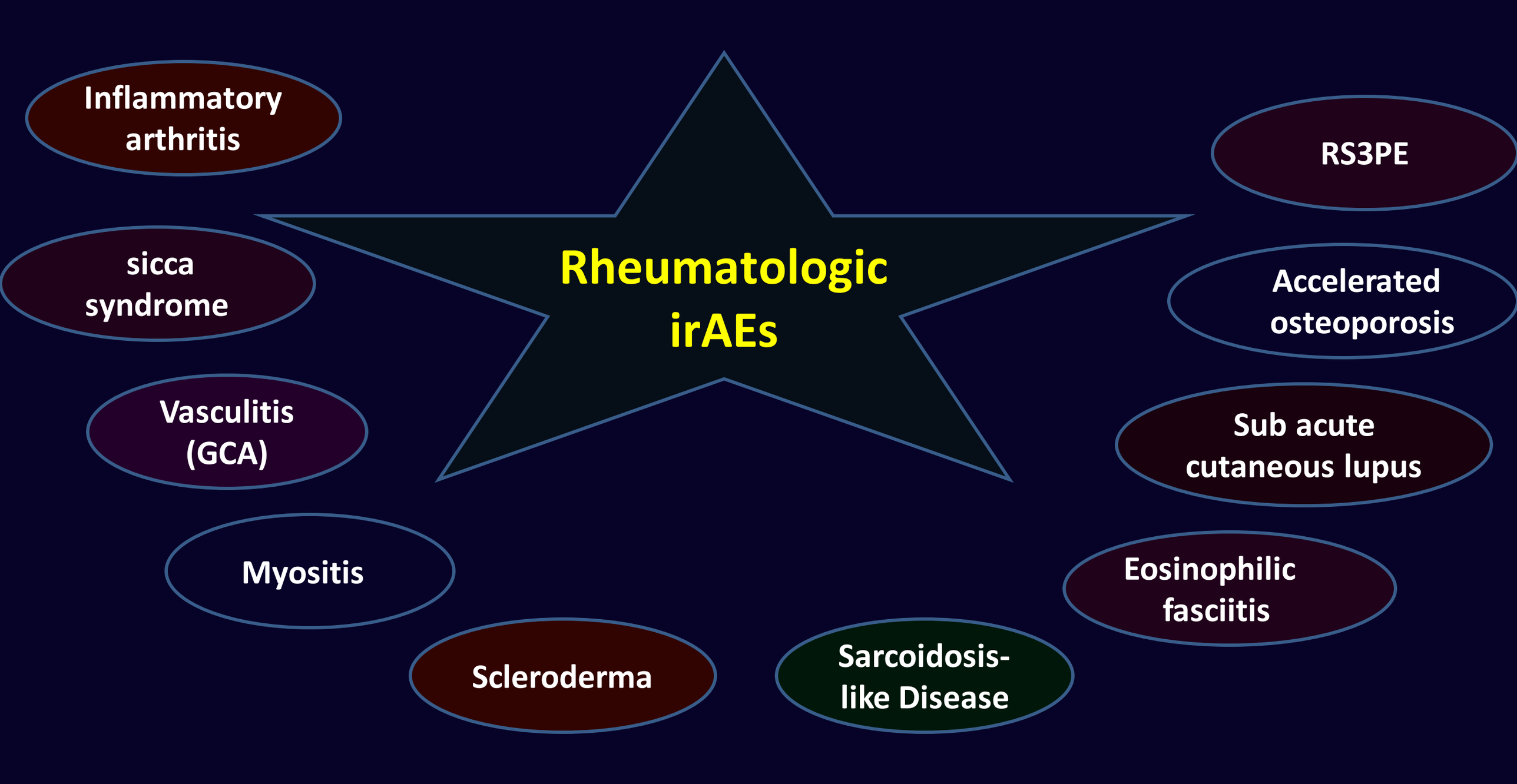
✓ **Hypophysitis :** hypophysitis is manifested by clinical symptoms of fatigue and headache. The diagnosis is established by low levels of the hormones produced by the pituitary

✓ **Adrenal insufficiency :** The most critical endocrinopathy

✓ **Autoimmune thyroid disease**

✓ **Type 1 diabetes mellitus**

- **PNEUMONITIS**
  - uncommon but potentially severe or fatal complication
  - a diagnosis of exclusion


Rheumatologic irAEs
Inflammatory arthritis
sicca syndrome
Vasculitis (GCA)
Myositis
Scleroderma
Sarcoidosis-like Disease
Eosinophilic fasciitis
Sub acute cutaneous lupus
Accelerated osteoporosis
RS3PE

Rheumatologic irAEs

➢ Epidemiology

- The **prevalence** of irAEs with rheumatologic phenotypes has not been well characterized in ICI clinical trial data.
- **Inflammatory arthritis** appears to be the most common rheumatic irAE , with estimates of prevalence ranging between 3% and 7% in retrospective studies.
- **Myositis** occurs in less than 1% of ICI-treated patients.
- The rates of giant cell arteritis , other types of vasculitis , sicca syndrome and scleroderma due to ICI therapy have not been well estimated.

Inflammatory arthritis

- the arthritis can develop at almost **any time** during ICI therapy , from two weeks to over a year from ICI initiation.

- **Several different clinical presentations :**

- ✓ **Small-joint polyarthritis** sometimes in a pattern similar to RA

- ✓ **Larger joint oligoarthritis** with or without inflammatory back pain , including a pattern similar to reactive arthritis

- ✓ **New-onset psoriatic arthritis** which has been reported in a patient on nivolumab

Inflammatory arthritis

- **tenosynovitis** and **enthesitis** has been reported by several groups
- **Reactive arthritis** with concomitant urethritis and conjunctivitis has also been described.
- Patients can rapidly develop **erosive disease** within months of symptom onset.
- inflammatory **back and neck pain** have been described in a limited number of patients

Inflammatory arthritis

- **monotherapy** with (PD-1) or (PD-L1) :
  - initial small joint involvement
  - inflammatory arthritis as their only irAE

- **combination therapy** with (CTLA-4) and PD-1 inhibition :
  - more likely to have arthritis that starts in the knee and to have a reactive arthritis phenotype.
  - another irAE
  - Higher Inflammatory markers

Inflammatory arthritis

➢ **LAB data :**

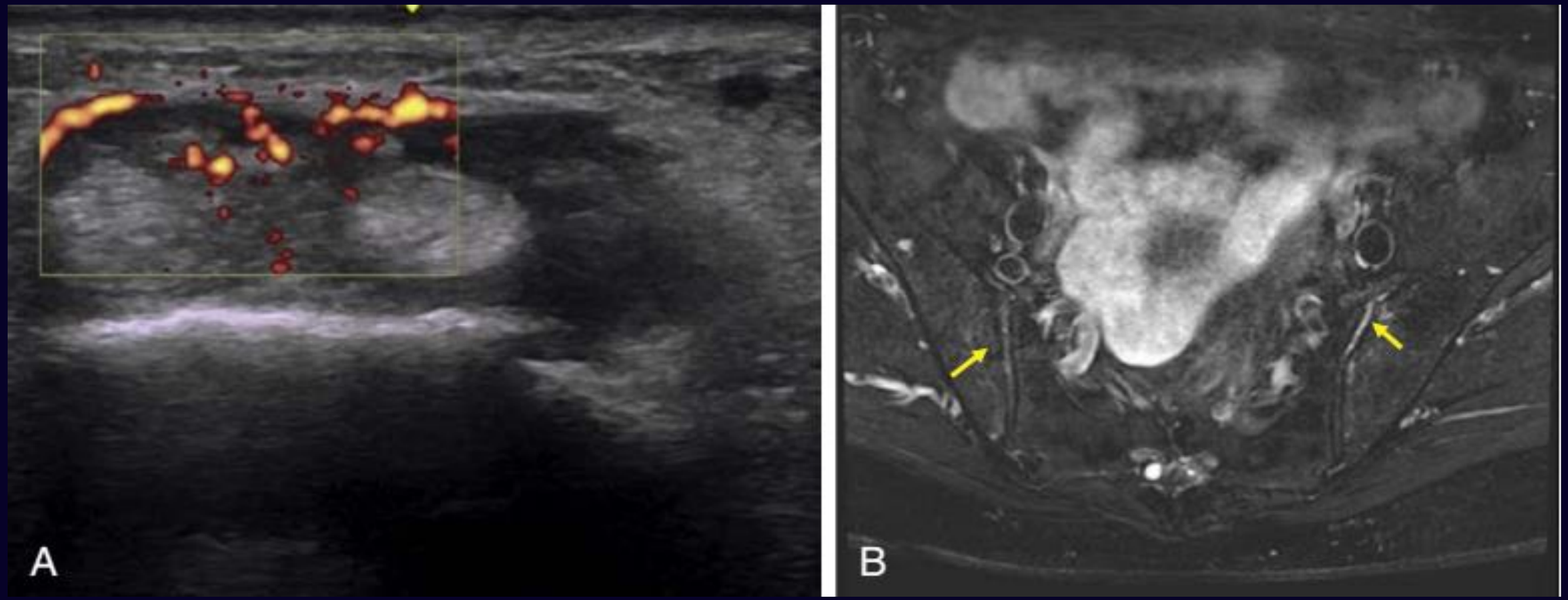
- Inflammatory markers
- ANA
- RF
- Anti ccp
- HLA B27

- **Risk factors** for developing ICI-induced inflammatory arthritis are largely unknown.
- It can occur with anti-PD-1, anti-PDL1, or combination PD-1/CTLA-4 inhibition.

- It has been noted in patients with a **variety of tumor types** from melanoma and NSCLC to prostate cancer and Hodgkin's lymphoma.

- A preliminary study suggests that possessing the **HLA DRB1 shared epitope allele** may be associated with developing ICI-induced inflammatory arthritis.

- inflammatory arthritis may persist after the cessation of ICI therapy and become a **chronic problem**.



- A) Doppler positive **tenosynovitis** of the wrist extensor tendons
- (B) Bilateral sacroiliac joint **synovitis** on MRI in a patient with inflammatory back pain

Inflammatory arthritis

➢ differential diagnosis

- Unrelated or coincidental presentations of a rheumatic disease
- Paraneoplastic syndromes
- Polyarthralgia due to medications or to fibromyalgia
- Bony metastasis causing erosive joint change

Inflammatory Arthritis : Treatment

➢ **mild cases** :

- NSAID
- very mild disease : topical NSAID
- In patients in whom NSAIDs should be avoided, or in whom a more rapid response is desired than expected with an NSAID , we use prednisone (initially 10 to 20 mg daily), then assess the response after one to two weeks
- intraarticular glucocorticoid injections
- Continue ICI

Inflammatory Arthritis : Treatment

➢ Moderate cases :

- Some patients will respond to 20 mg prednisone daily, but others will need much higher doses, up to 1 mg/kg.
- If a patient is on less than 10 to 20 mg daily of prednisone , many oncologists will often continue the ICI rather than hold it.
- If steroids cannot be weaned to a low dose or of in 4 to 6 weeks, then other immunosuppressive agents will be used.

Inflammatory Arthritis : Treatment

- The **choice of agent** depends on the **severity** and clinical features of the arthritis , any **other irAEs** the patient has currently or had previously , and **plans** for future ICI use/other cancer treatments.

- If the patient is still having symptoms of inflammatory arthritis 3 months or longer after ICI cessation at presentation with no plans for retreatment , it may make sense to start with methotrexate or leflonomide for moderate cases or hydroxychloroquine or sulfasalazine for more mild cases.

- Anti TNF and Tocilizumab

Inflammatory Arthritis : Treatment

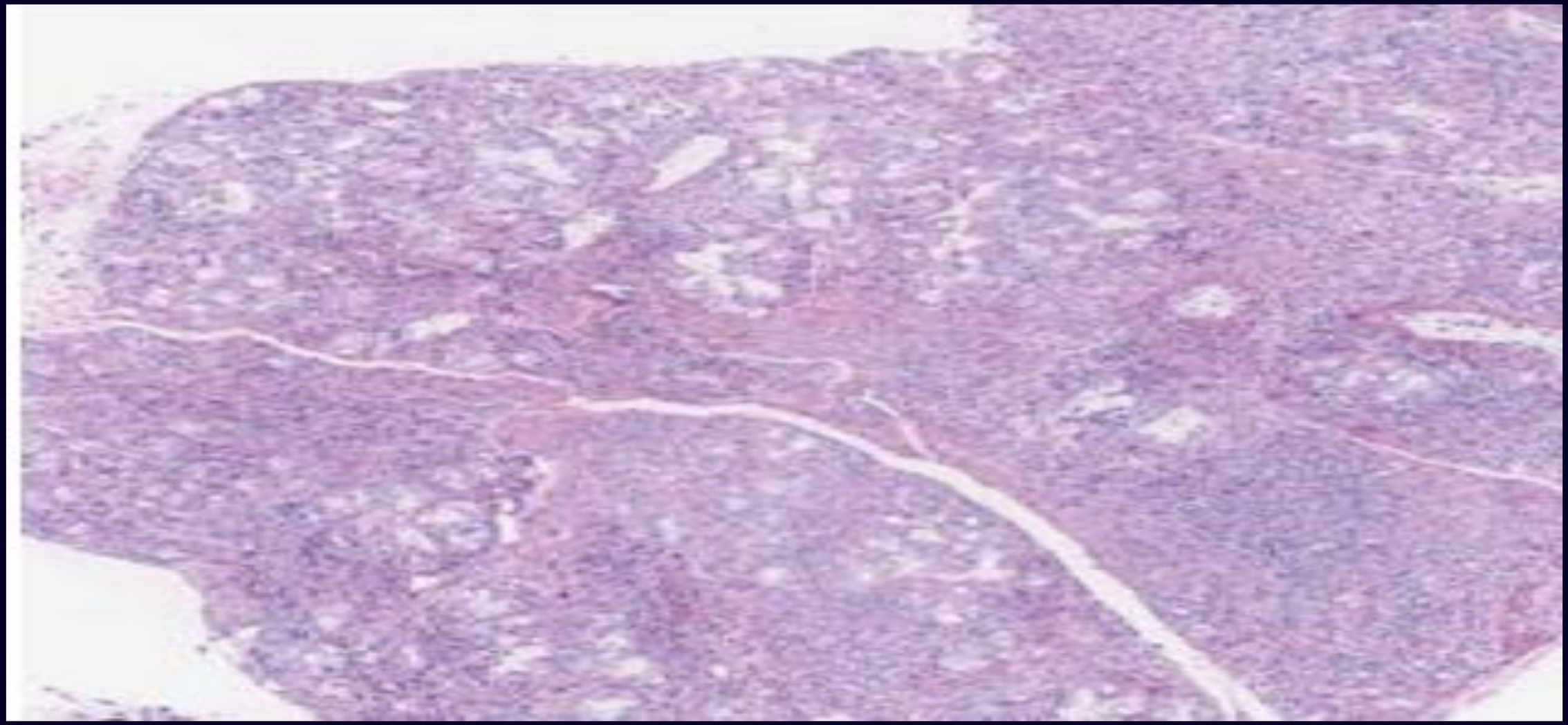
➢ Severe arthritis :

- In selected patients with severe arthritis who are **refractory** to glucocorticoid therapy or **unable to wean** to low-dose glucocorticoids , we use a TNF inhibitor

- **TNF inhibitors** may be preferred over conventional DMARDs in patients in whom it is undesirable to wait for several weeks for a response to MTX or other conventional synthetic DMARDs or in whom **comorbidities** (liver disease, cytopenias) may preclude use of such agents

Sicca Syndrome

- There have been reports of dry mouth and dry eyes, often severe, occurring in the setting of ICI therapy . **Dry mouth** is commonly the most prominent symptom.
- parotitis
- sensory neuropathy
- anti-Ro or anti-La antibodies
- Biopsies of the minor salivary gland ?



Minor salivary gland biopsy from a patient with ICI-associated autoimmune sialadenitis

sicca syndrome : Treatment

- In sicca syndrome, treatments have been primarily **symptomatic** , focusing on dry eyes and dry mouth.

- **parotid gland swelling** : prednisone at doses of 1 0 to 40 mg daily tapered off over weeks

- Treatment of **more severe oral manifestations** was described in one series : ICI therapy was discontinued either temporarily or permanently in the majority of patients.The authors advised that for patients with grade 2 or 3 symptoms **ICI therapy should** be held and **prednisone 20 to 40 mg** daily should be prescribed for two to four weeks, followed by a taper

PMR/GCA

- **Isolated PMR** is the more common presentation . There has been a description of a clinical syndrome with PMR features and smaller joint involvement of inflammatory arthritis.
- PMR and GCA have been seen with both CTLA-4 and PD-1 inhibition.
- age
- Inflammatory markers ?
- Temporal artery biopsy is important if GCA is suspected

PMR/GCA : treatment

- **GCA :** we use standard or slightly **higher doses of prednisone** (50 to 60 mg daily)
- intravenous corticosteroids are often used initially
- the ICI has been held during initial treatment or discontinued because of the high dose of glucocorticoids required for the initial treatment of GCA.
- The role of biologic agents such as tocilizumab ?

- **PMR :** we advise starting doses of prednisone for PMR of 1 5 to 25 mg daily initially, followed by a gradual taper.
- these patients generally would not necessitate discontinuation of the ICI.
- In one series of 20 patients with ICI-induced PMR, **tocilizumab** was used as a glucocorticoid-sparing agent in two patients

Other Vasculitis

- single organ vasculitis affecting the uterus and retina
- systemic ANCA-associated vasculitis
- aortitis and periaortitis

Myositis

- Inflammatory myopathies due to ICIs : rare
- Most cases are more similar to polymyositis with **no classic skin rashes** of dermatomyositis; however, several cases of dermatomyositis have occurred.

- cases have been seen with both CTLA-4 and PD-1/PD-L1 blockade.

- **Proximal muscle weakness** is the most common presentation, but distal weakness, respiratory weakness, neck weakness, and concomitant myocarditis have been seen.
- **Rhabdomyolysis** can occur in some patients.
- The myositis may also be accompanied by **fasciitis**

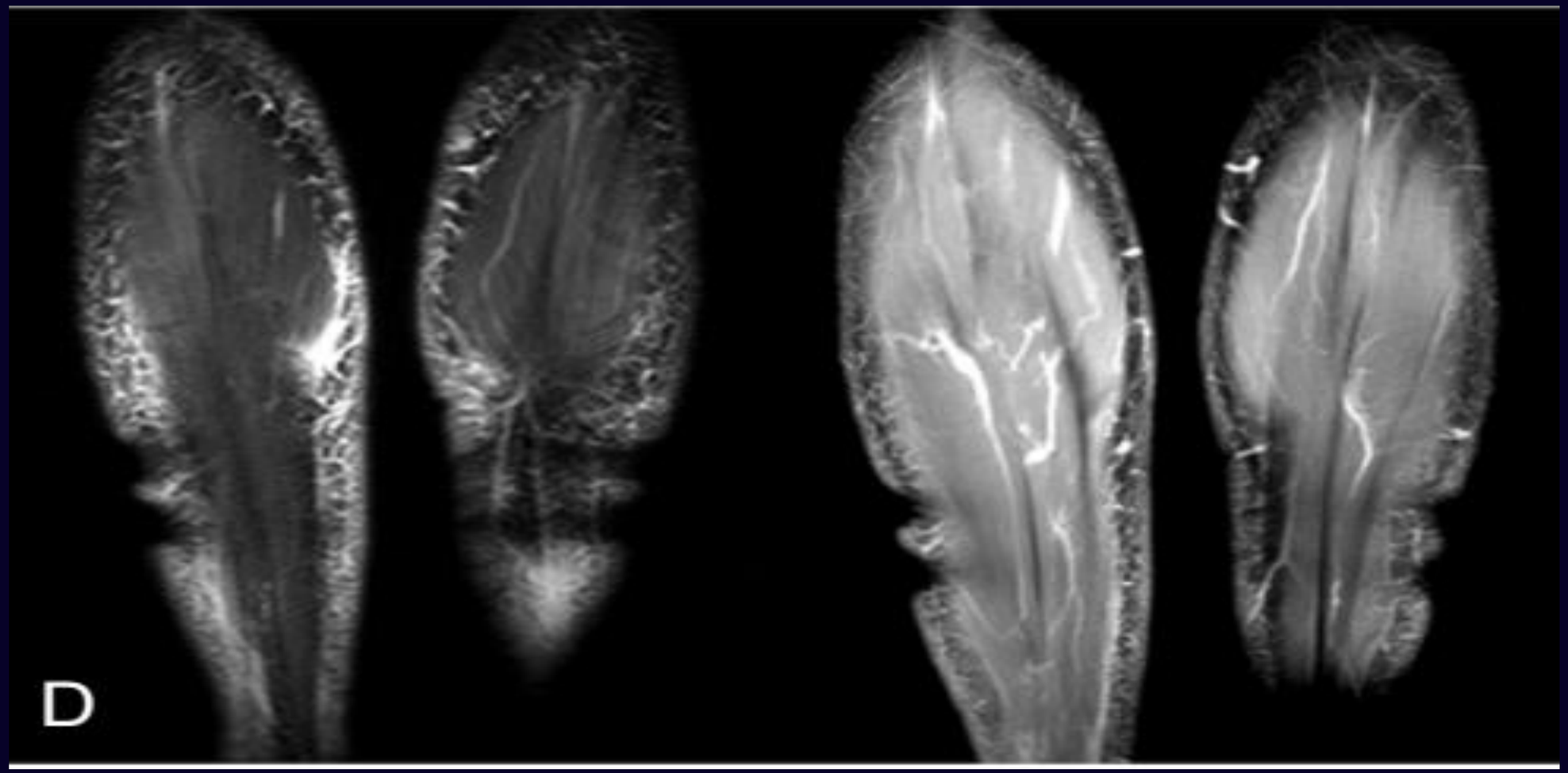
Myositis

- Creatinine kinase levels are elevated, ranging from 500 to over 16,000 U/L.
- MRI
- Electromyography
- Muscle biopsies : endomysial inflammation primarily , necrotizing myopathy,
- Myositis-specific antibodies

Myositis

- **Risk factors :** One study showed that pre-existing anti-acetylcholine receptor antibodies and lymphopenia were associated with developing myositis after PD-1 treatment.

- Additionally , patients with myasthenia gravis/myositis overlap and myocarditis overlap have been described; this is especially important to remember in patients presenting with respiratory compromise



- Muscle MRI from myositis : Coronal STIR (left) and fat-suppressed contrast-enhanced T1-weighted MRI (right) show **focal changes of myositis and fasciitis** of the right gastrocnemius and soleus . There are also subcutaneous edematous changes.

Myositis : treatment

- **glucocorticoids** have been the mainstay of treatment.
- Initial doses of prednisone from 30 mg daily up to 1 gram of intravenous methylprednisolone have been used, followed by gradual glucocorticoid tapers
- ICIs have been discontinued in all published cases.
- In severe or refractory cases of myositis, **IVIG** has been used, and **plasmapheresis** has been attempted with some limited success

Scleroderma

- A small number of cases of **scleroderma-like skin changes** with diffuse and limited skin involvement have occurred
- One of these cases with diffuse skin involvement had a modified Rodnan Skin Score of 28, which improved with prednisone and mycophenolate.
- internal organ involvement ?

- autoantibodies ? In three cases where autoantibodies were tested, the patients were negative for anti-nuclear, anti-centromere ,anti ribonucleoprotein,and anti-topoisomerase antibodies.

- acral vascular syndrome

Sarcoidosis-like Disease

- Most reported cases in ICI-induced sarcoid-like disease have both pulmonary and skin involvement.
- The **pulmonary involvement** has included hilar and mediastinal lymphadenopathy and interstitial infiltrates (groundglass opacities, interstitial thickening).
- **Skin lesions** have been erythematous papules or nodules, showing granulomatous inflammation when biopsied.

- To date, there are no reports of sarcoid arthropathy, hepatic involvement, or other organ involvement due to ICIs

- **RS3PE** (remitting seronegative symmetric synovitis with pitting edema)
- **Eosinophilic fasciitis**, occurred in a patient treated with pembrolizumab
- **Accelerated osteoporosis** leading to compression fractures and focal bone resorptive lesions
- **Sub acute cutaneous lupus**
- **lupus nephritis** occurring due to ICI therapy

Drug	Rheum irAEs Where Drug May Be Effective
Hydroxychloroquine	Inflammatory arthritis Cutaneous lupus
Sulfasalazine	Inflammatory arthritis
Methotrexate	Inflammatory arthritis
Leflunomide	Inflammatory arthritis
TNF inhibitors Infliximab Adalimumab Etanercept	Inflammatory arthritis
IL-6R inhibitors Tocilizumab Sarilumab	Inflammatory arthritis PMR GCA
Secukinumab	Inflammatory arthritis Psoriasis
Ustekinumab	Inflammatory arthritis Psoriasis
Apremilast	Inflammatory arthritis Psoriasis
Intravenous immunoglobulin	Myositis
Mycophenolate	Myositis
Azathioprine	Myositis
Rituximab	Myositis Inflammatory arthritis
Abatacept	Inflammatory arthritis
Tofacitinib	Inflammatory arthritis

Potential Immunomodulatory Agents for Treatment of Rheumatologic irAEs

Pre-existing Autoimmune Disease and ICI Use

- Approximately one-third or more of patients with preexisting rheumatic or other systemic or autoimmune disease have experienced **flares** of their prior disorder in association with treatment using (ICIs)
- Many have been successfully managed with glucocorticoids or other treatments, but some have required discontinuation, usually temporarily, of their ICI

Pre-existing Autoimmune Disease and ICI Use

- A systematic literature review of retrospective studies and case reports included 123 patients with pre-existing autoimmunity .
- In this study, 75% had an **exacerbation**, 25% had a de novo irAE , but only 17.1% had to discontinue ICI therapy due to flare or irAE.
- In general the rate of exacerbations was higher with PD-1/PD-L1 inhibition, while the rate of de novo irAEs was higher with CTLA-4 inhibition.

- though there are limited data regarding use of ICIs in patients with autoimmune disease , they seem to be **generally well tolerated** and flares rarely lead to discontinuation of therapy.

- To manage patients with pre-existing autoimmune disease and advanced cancer on ICI therapy , multidisciplinary care and communication are key.

Concerns With Immunosuppression

- There are theoretical concerns that treating irAEs with immunosuppression will negatively impact the tumor response.
- There is emerging evidence that the use of corticosteroids at the **onset of ICI** therapy may be detrimental.
- In a study of patients being treated with antiPD-1 and anti-PD-L1 agents for NSCLC, baseline use of 10 mg of prednisone or greater daily was associated with worsened overall response rate, progression-free survival, and overall survival.
- Information is lacking on whether being on **immunomodulatory medications** affects tumor response to ICIs due to the small numbers of patients and the heterogeneity of immunomodulatory treatment.


Thank you for
your attention