Immunotherapy-induced rheumatic autoimmune disorders

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The incidence of immunotherapy-induced rheumatic autoimmune disorders (IRAES: rheumatic immune-related adverse events) is estimated at 5%-6.6%. They appear to be more common with anti-CTLA-4 therapy than with anti-PD-1 therapy. The risk is even higher in combined or sequential CTLA-4/PD-1 therapy compared to monotherapy.
In most cases, they usually appear in the first 12 weeks after the start of treatment (70% of cases in the first 8 weeks). Around 40-50% of patients with IRAES also present with other non-rheumatic immune-related adverse events. As with other immune-mediated complications, it is speculated that the onset of IRAES would be associated with a better anti-tumour response.

The most common IRAES reported are arthritis, symptoms similar to polymyalgia rheumatica, Sjögren's syndrome (dry syndrome) and different types of myopathy. Except for the management of myopathies, immunotherapy will always be maintained for all other rheumatic complications whenever possible if it is effective.

Leaving aside arthralgias (the frequency of which in clinical trials ranges from 5% to 16%), arthritis is the most common rheumatological complication of immunotherapy. In more than half of cases, clinical symptoms of undifferentiated arthritis in the form of oligo or polyarthritis, often asymmetric, not deforming or erosive, and transient, usually manifest. On other occasions, arthritis becomes chronic and adopts the pattern of a well-defined systemic autoimmune disease, the most common being rheumatoid arthritis (40%) and spondyloarthropathies, principally psoriatic arthropathy and reactive arthritis with ocular involvement and urethritis. In these cases, there are some differences with the classic forms of these diseases. Immunotherapy-induced rheumatoid arthritis occurs equally in both sexes, is usually seronegative (positivity of rheumatoid factor: 12%; positivity of anti-cyclic citrullinated peptide antibodies: 27%), manifests from the onset of the disease with significant involvement of the flexor and extensor tendons of the hands and is generally erosive (with early onset of erosions). Cases of spondyloarthropathy are not associated with HLA-B27, also cause early erosions and, in the case of psoriatic arthropathy, it is not uncommon for articular symptoms to precede the onset of psoriasis. The starting treatment for arthritis in patients on immunotherapy is non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids (prednisone or methylprednisolone) at medium or low doses. In the case of persistence or ineffectiveness, hydroxychloroquine or methotrexate will be added. In refractory patients, biological rescue treatments have been trialled (principally TNF alpha antagonists, particularly infliximab, and tocilizumab),

without the preliminary evidence available to date demonstrating an increased risk of infectious adverse effects or loss of efficacy in anti-tumour response in these patients. Polymyalgia rheumatica-like cases have been reported, particularly in relation to anti-PD1 therapies. Unlike classical polymyalgia rheumatica, acute-phase reactants are not always elevated and arthritis plays a major role in rhizomelic clinical symptoms. They tend to respond well to glucocorticoids, although sometimes medium or high doses are needed to achieve clinical remission. In cortico-dependent cases (patients who relapse with low doses of prednisone), methotrexate appears to be effective. Although rare, some cases have been described of polymyalgia rheumatica associated with giant cell arteritis confirmed by temporal artery biopsy, so this possibility should be taken into account in the assessment of these patients.

Sjögren's syndrome that manifests as a complication of immunotherapy is usually acute and has a rapidly progressive course. Oral dryness is as or more pronounced than ocular dryness, which may be absent. Unlike Sjögren's syndrome, the specific immunology (anti-Ro antibodies) is negative and the onset of parotid enlargement is very rare. It usually responds partially or completely to glucocorticoids at medium/low doses and to sialogogues (pilocarpine).

Different types of myositis have been reported as a complication of immunotherapy. The most common is polymyositis. Some cases of dermatomyositis, myofascitis (simultaneous inflammation of the muscular fascia and of the proximal and distal muscles of the lower extremities) and necrotising myopathy have also been documented. Broadly speaking, the elevation of muscle enzymes in these patients is usually very marked (CPK x 10-100 IU/l). In addition to the involvement of the proximal musculature, cases of respiratory compromise have been described, some of them fatal, and with involvement of the ocular muscles. The concomitant presence of myocarditis in these patients is also common (32%). For its diagnosis, imaging tests and muscle biopsy, which usually shows typical findings, are useful. To manage this complication, in addition to high-dose glucocorticoids and immunosuppressants, the temporary suspension of immunotherapy is usually necessary. These patients respond less to intravenous immunoglobulins.

Finally, different autoimmune diseases, seemingly induced by immunotherapy, have been reported, principally sarcoidosis (with pulmonary, cutaneous, muscular and central nervous system involvement), as well as cases of systemic sclerosis, eosinophilic fasciitis, lupus nephritis, vasculitis other than giant cell arteritis (granulomatosis with polyangiitis and single organ vasculitis affecting the central nervous system, retina or uterus), Vogt-Koyanagi-Harada-like disease, RS3PE syndrome and paraneoplastic acral vascular syndrome. Similarly, the exacerbation of a pre-existing autoimmune disease with immunotherapy has been documented, which is particularly common in psoriasis, although it has also been reported in patients with rheumatoid arthritis, polymyalgia rheumatica, primary Sjögren's syndrome and autoimmune thrombocytopenic purpura. In most cases, the flare-up of activity is usually of mild to moderate intensity and is generally transient. This must be taken into account when assessing the risk/benefit of the indication in patients with an underlying autoimmune disease, but it is not a priori an absolute contraindication for immunotherapy.