Drug-induced rheumatic syndromes: the need to be aware

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Drug-induced rheumatic syndrome is a challenging and often difficult to diagnose entity but remains a neglected part of our scientific discussions. Advances in modern medicine with innovative technologies and novel drug discovery coupled with polypharmacy, in search of optimal health, has led to an increase in drug-induced diseases. These are often misdiagnosed and inadequately treated. They can mimic numerous rheumatological disorders, which is often difficult to attribute to one particular drug. The insidious onset of symptoms along with long duration of drug intake further adds to the complexity. Detailed history taking, temporal profile of clinical manifestations and high index of suspicion would be valuable tools to identify drug-induced autoimmune diseases. A thorough knowledge about various drug-induced rheumatic syndromes is of utmost importance in order to avoid unnecessary investigations and inappropriate therapy.

Drug-induced vasculitic-like presentations have been identified as a distinct entity and have the potential to involve any vessel.[1] The importance of this is highlighted by the fact that drug-induced vasculitis has been classified as a separate group in the Chapel Hill Consensus Conference 2012 definitions of vasculitis.[2] Although nonsteroidal anti-inflammatory drugs and antibiotics are commonly implicated in cutaneous leukocytoclastic vasculitis, severe necrotising vasculitis with antineutrophil cytoplasmic antibody (ANCA) positivity due to cocaine alone or when adulterated with levamisole, anti-thyroid drugs, such as propylthiouracil, hydralazine and minocycline, is also well known. The vasculitis associated with cocaine use is usually both myeloperoxidase (MPO)- and PR3-ANCA positive,[3] whereas cocaine adulterated with levamisole manifests as MPO- and PR3-ANCAs, human neutrophil elastase-ANCAs and antinuclear antibody positive.[4] The proposed mechanisms include immune complex deposition, neutrophil extracellular traps and bypassing of immune checkpoints.[1] Newer anticancer therapies including immune checkpoint inhibitors can also cause vascular injury, even of the large vessels.[5] Besides withdrawal of the drug, many patients require immunosuppressive therapy including corticosteroids and/or cyclophosphamide for treatment.

There is an ever-expanding list of medications with the potential to cause lupus-like manifestations. Among these, procainamide and hydralazine have the highest risk of developing drug-induced lupus erythematosus (DILE), whereas quinidine is associated with a moderate risk.[6] Antihypertensives such as methyldopa, antitubercular drugs such as isoniazid, and others namely sulfasalazine and carbamazepine have also been implicated in the development of DILE, although with a lower risk. Anti-tumour necrosis factor (TNF) agents, often used to control arthritis, are also implicated in DILE.[7] The clinical features of DILE are often similar to systemic lupus erythematosus (SLE), thus distinguishing the two becomes challenging. The common manifestations of DILE include fever, myalgia, arthralgia and skin lesions. Severe disease with renal and neurologic involvement is extremely rare. Erythema multiforme is more common in DILE than in SLE. The mechanisms implicated are loss of central tolerance, molecular cross-reactivity and epigenetic modifications.[6] Timely identification and early withdrawal of the offending drug are essential for improved outcomes.

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Several drugs are implicated in causation of myopathy and can range from mild muscle aches and asymptomatic rise in serum creatine kinase to severe rhabdomyolysis.[8] Some drugs commonly used in rheumatology that cause varying severity of muscle involvement include glucocorticoids, colchicine, antimalarials and TNF inhibitors. Besides these, statins also can cause nonspecific muscle pain, proximal myopathy and severe necrotising myopathy. Timely withdrawal of the drug helps in reversal of symptoms.

Drug-induced osteomalacia and osteoporosis are also well described. Anti-epileptics, proton pump inhibitors, glucocorticoids, heparin, immunosuppressants and anticancer drugs are some of the commonly used drugs associated with bone loss. Early identification, vitamin D and calcium supplementation, and using bisphosphonates are some of the measures to prevent morbidity.

Drugs can also cause scleroderma-like conditions, including morphea, linear scleroderma and diffuse scleroderma. Bleomycin and pentazocine are among the prototype drugs. Immune checkpoint inhibitors can cause systemic sclerosis-like disease.[9] Antineoplastic drugs (bleomycin), disease-modifying antirheumatic drugs (methotrexate, leflunomide, TNF inhibitors) and amiodarone can cause pulmonary fibrosis, which in a background of connective tissue disorders such as rheumatoid arthritis often becomes difficult to ascertain the causality.

Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN)/DRESS (drug reaction with eosinophilia and systemic symptoms) are characterised by widespread epidermal and/or mucosal detachment that may also be drug induced. These are commonly precipitated by drugs such as carbamazepine, phenytoin, lamotrigine, allopurinol and co-trimoxazole. It is pertinent to note that Stevens-Johnson syndrome may be a manifestation of SLE itself, further confounding the diagnosis. Drug-induced SJS/TEN usually have acute presentation with involvement of palms and soles being uncommon and there are no immunofluorescence deposits at dermoepidermal junction on skin biopsy.[10]

Adjuvants commonly used in vaccines to increase their efficacy have been associated with the autoimmunity/autoinflammatory syndrome induced by adjuvants (ASIA syndrome). It was first identified by Shoenfeld et al.[11] in 2011 to include a variety of conditions, such as siliconosis, macrophagic myofasciitis syndrome, sick building syndrome, Gulf war syndrome and post-vaccination autoimmune phenomena, all of which were triggered after adjuvant exposure.

Drugs are also implicated in various musculoskeletal and soft tissue rheumatism syndromes. The most common of these being hyperuricemia and gout after use of anti-tubercular drugs and diuretics. Drugs like fluoroquinolones can precipitate periarticular disorders such as tendinopathies.[12]

In this context, we would like to draw the attention of readers towards the 'Drug-Induced Rheumatic Syndromes' supplement of the *Indian Journal of Rheumatology* published in December 2019.[13] The various drugs implicated in autoimmune disorders are systematically discussed in the supplement to bring about awareness among physicians and rheumatologists. Early withdrawal of the offending drug and immunosuppressive therapy in some cases are pivotal for better outcomes.

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