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of mycophenolate compared to other immunosuppressive agents is the lack of renal or hepatic toxicity. Rituximab Rituximab is a monoclonal antibody directed against CD20+ B cells. A large randomized controlled trial found no benefit, but there were flaws in the study design. Most authorities feel that rituximab can be beneficial in some patients who are refractory to prednisone and at least one of the other second-line agents. The typi cal dosage is 750 mg/m2 (up to 1 g) IV with a second infusion 2 weeks later and with repeat courses (375 mg/m2 as a single infusion or with a second infusion 2 weeks apart) every 6–18 months as needed. Drugs in Clinical Trials Trials of a monoclonal antibody to block IFN-β and drugs to target downstream pathways (e.g., JAK-1) are ongoing in DM and other forms of myositis. Studies targeting the neo natal Fc receptor (FcRn) to decrease myositis-specific antibodies are underway in DM, ASyS, and IMNM, as are trials with chimeric antigen receptor (CAR) T-cell therapy. Ongoing trials in IBM include rapamy cin as well as a trial of a monoclonal antibody binding to KLRG1 to deplete highly differentiated muscle-invading T cells. MYOSITIS ASSOCIATED WITH CHECKPOINT INHIBITORS Autoimmune neurologic complications, including inflammatory neu ropathy (Chap. 458), myasthenia gravis (Chap. 459), and myositis, can occur with use of immune checkpoint inhibitors (anti-CTLA-4, antiPD-1, and anti-PD-L1) to treat various cancers. Patients with myosi tis often develop muscle pain and weakness (axial musculature and proximal limbs) after one or two cycles. Myocarditis can also develop. Additionally, diplopia with extraocular weakness along with dysphagia and dysarthria suggesting the co-occurrence of myasthenia gravis (MG) may be present. In such cases, an elevated CK level helps sup port the diagnosis of myositis, while acetylcholine receptor antibod ies or decremental response on slow repetitive nerve stimulation can establish the diagnosis of MG. Endomysial inflammatory cell infiltrates composed of macrophages expressing PD-L1 and CD8+ lymphocytes expressing PD-1, overexpression of MHC-I on sarcolemma of muscle fibers, and scattered necrotic and regenerating fibers can be found on muscle biopsies. The immune checkpoint inhibitor should be discontinued, but most patients require concurrent treatment with glucocorticoids or IVIG. Patients generally improve over several months, during which time immunotherapy can be tapered. There are rare reports of patients with mild myositis who were able to be successfully re-treated with an immune checkpoint inhibitor. MYOSITIS ASSOCIATED WITH COVID-19 INFECTION Early series of patients hospitalized with COVID-19 report that as many as 44% of patients experience muscle pain or fatigue and 33% have elevated CK levels. Rare cases are complicated by myoglobinuria. Histopathology can demonstrate inflammatory cell infiltration and necrotic muscle fibers. In autopsy series, SARS-CoV-2 has not been demonstrated in muscle fibers, and the

myositis is felt in most, if not all, to be due to cytokine storm. Whether COVID-19 infection can induce a chronic autoimmune myositis is controversial; there have been a number of reports of various types of IM, some with MSA, in patients following COVID-19 infection, but temporal associations do not equal causation. GLOBAL ISSUES There is a lack of epidemiologic data with regard to the incidence and prevalence of various subtypes of IM throughout the world. Compli cating the issue is disease awareness and the inability to obtain and process muscle biopsies and MSAs, particularly in less developed countries. Nevertheless, each of these disorders occurs throughout the world. The specific environmental triggers and genetic risk factors are likely variable. Interestingly, a report from Japan found that 28% of IBM patients had evidence of exposure to hepatitis C, which was much higher than seen in the Western Hemisphere and also more common

than seen in PM and healthy population controls in Japan. HIV-associated PM and IBM are more commonly encountered in areas endemic for HIV, and recent studies suggest most of these “PM” patients turn out to have IBM and can develop symptoms at an earlier age (e.g., in the 30s). Interestingly, while most cases of anti-HMGCR myopathy in North America and Europe are associated with prior statin use, the major ity of such cases in Asia are not. Pyomyositis and parasitic myositis are clearly more common in the tropics. The prevalence of different types of cancers varies in different parts of the world, an important consideration with respect to paraneoplastic myositis. For example, nasopharyngeal cancer is particularly common in Asia; thus, assess ment for this type of cancer should be considered in the workup of patients from high-risk regions.

CHAPTER 378 Relapsing Polychondritis ■ ■FURTHER READING Aggarwal R et al: ProDERM Trial Group. Trial of intravenous immune globulin in dermatomyositis. N Engl J Med 387:1264, 2022. Allenbach Y et al: Immune-mediated necrotizing myopathy: Clinical features and pathogenesis. Nat Rev Rheumatol 16:689, 2020. Amato AA, Russell JA (eds): Neuromuscular Disorders, 2nd ed. New York, McGraw-Hill Education, 2016, pp. 827–871. Britson KA et al: Loss of TDP-43 function and rimmed vacuoles persist after T cell depletion in a xenograft model of sporadic inclusion body myositis. Sci Transl Med 14:eabi9196, 2022. Greenberg SA: Inclusion body myositis: clinical features and patho genesis. Nat Rev Rheumatol 15:257, 2019. Julien S et al: Immune-mediated necrotizing myopathy (IMNM): A story of antibodies. Antibodies (Basel) 13:12, 2024. Mariampillai K et al: Development of a new classification system for idiopathic inflammatory myopathies based on clinical manifestations and myositis-specific autoantibodies. JAMA Neurol 75:1528, 2018. Müller F et al: CD19 CAR T-cell therapy in autoimmune disease: A case series with follow-up. N Engl J Med 390:687, 2024. Pinal-Fernandez I et al: Pathogenic autoantibody internalization in myositis. medRxiv [Preprint]. 17:2024.01.15.24301339, 2024. Puwanant A et al: Clinical spectrum of neuromuscular complications after immune checkpoint inhibition. Neuromuscul Disord 29:127, 2019. Suh J et al: Skeletal muscle and peripheral nerve histopathology in COVID-19. Neurology 97:e849, 2021. Marcela A. Ferrada, Peter C. Grayson

Relapsing Polychondritis Relapsing polychondritis (RP) is a rare systemic disease characterized by recurrent inflammation in cartilaginous structures. Involvement of the ears, nose, respiratory tract, and joints are hallmark features of the disease; however, other organs can be affected including the eyes, inner ear, nervous system, skin, and cardiovascular system. Some patients with RP may be concomitantly diagnosed with other rheumatologic diseases, such as Sjögren’s syndrome or

systemic lupus erythematosus. Recurrent chondritis of the ears and nose in older male patients with severe systemic inflammation and progressive bone marrow failure is associated with acquired hematologic mutations in UBA1, a condition now known as the VEXAS (vacuoles, E1 enzyme, X-linked, autoin flammatory, somatic) syndrome. Prompt recognition and accurate diagnosis of RP or VEXAS syndrome are essential to prevent lifethreatening complications of these diseases. The epidemiology of RP is poorly characterized. The disease is commonly reported to primarily affect middle-aged adults without a strong sex predilection; some cohort studies report female predilection,

but large, population-based studies typically show equal sex distribu tion. Children can be affected; however, these data are limited to case reports. Rare instances of familial aggregation have also been reported. The estimated incidence rate of disease is 0.7–3.5 cases per million per year, and prevalence estimates range from 4.5–25 cases per million. Epidemiologic data in RP are limited to older studies, typically evalu ating population distributions more than three decades ago in cohorts from Europe and North America. Given the diagnostic challenges encountered in this condition, these data may underestimate the true prevalence of disease. Although RP has been reported in many regions of the world, whether racial or ethnic differences are associated with variable clinical features or outcomes is not known.

PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders ■ ■PATHOLOGY AND PATHOPHYSIOLOGY Histologic findings from biopsy of affected cartilage are dependent on the timing of tissue sampling. In acute disease, a mixed inflammatory infiltrate of myeloid and lymphoid populations is observed at the car tilage interface. Over time, cartilage destruction is marked by lacunar breakdown and loss of chondrocytes, replaced by fibrosis. Biopsy of affected cartilage may cause morbidity, and there are no features on histology that are specifically diagnostic for RP. Therefore, biopsy is often reserved when there is a high suspicion of conditions that mimic RP, particularly infectious diseases and malignancies. Although genetic, environmental, and immunologic aspects of the disease have been studied in humans and in animal models, the exact mechanisms that drive the disease are unclear. Limited studies in animal models support the concept that autoimmunity to cartilage components may play a role in RP. Immunization of specific animals to type II col lagen, type IX collagen, or matrillin-1 can recapitulate various aspects of the clinical phenotypes observed in patients with RP; however, the performance characteristics of these antibodies in clinical practice are poor to differentiate RP from other diseases. Autoantibodies to type II collagen have been reported in small cohorts of patients with RP but are neither sensitive nor specific to be considered as an acceptable diag nostic marker of disease. Observational cohort data suggest that B-cell– depleting therapies are not particularly effective to treat the condition, arguing against a strong primary role of antibody-mediated disease. Acute phase reactants (e.g., erythrocyte sedimentation rate or C-reactive protein) are not reliably elevated in patients with RP. Proinflammatory cytokines and chemokines related to both innate and adaptive immunity have been identified in association with RP; A FIGURE 378-1 Representation of ear involvement in relapsing polychondritis. A and B. Examples of typical ear chondritis, with significant inflammation of the pinnae. C. Mild ear cartilage inflammation. D. Cartilage damage.

however, these findings are not consistent and, therefore, are not rou tinely measured to guide management in clinical practice. ■ ■CLINICAL MANIFESTATIONS AND

ORGAN INVOLVEMENT RP is associated with a wide range of clinical manifestations. In the absence of a diagnostic blood test, a detailed medical history and physical examination are the most essential tools for diagnosis and, most importantly, further management. Because disease activity is intermittent and patients may not exhibit clear signs of inflammation during direct evaluation, it is crucial to consider the patient's symptoms over time and to review any provided photographic documentation of disease features. Ears, Nose, and Throat Ear involvement is one of the most common clinical manifestations of relapsing polychondritis, affecting 80–90% of the patients. However, there are no clear definitions of ear chondritis, and patient descriptions of pain and associated symptoms are variable. The typical description includes involvement of only the cartilaginous aspect of the ear (pinnae) (Fig. 378-1A and B). However, a subset of patients may report pain in the ears with minimal associ ated findings visualized on physical examination, such as mild swell ing or erythema (Fig. 378-1C). Although damage to the cartilaginous portion of the external ear (i.e., "cauliflower ear") is observed in RP

(Fig. 378-1D), it is present only in a small number of patients, usually in the setting of recurrent episodes of ear inflammation. Questions that can be helpful to elicit the nature of ear pain include asking about onset, duration, and triggers. Common triggers include minimal trauma to the ear (such as from lying on the effected side or wearing glasses) or temperature changes. Patients usually describe a sensation of pressure at the bridge of the nose that may not be accompanied by other associated symptoms. Some patients may have overt redness and swelling of the bridge or tip of nose, but this is less common (Fig. 378-2A). While a "saddle nose" has been described as a typical clinical finding in RP, many patients will not develop an obvious nasal deformity (Fig. 378-2B). The nasal septum and nasal passages should always be evaluated in patients with suspected RP, as many patients can have septal ulcers and mucosal inflammation. In contrast to granulomatosis with polyangiitis (GPA) where a saddle nose deformity is usually associated with a septal perforation (Chap. 375), patients with RP who have a saddle nose deformity usually do not have B

C FIGURE 378-1 (Continued) a septal perforation, as most of the nasal perforations in patients with RP are located anteriorly. Patients can have complaints of throat pain or a sensation of globus, usually described as a "choking sensation." Patients can also report pain on the anterior aspect of the neck, in some cases associated with erythema, usually located at the level of the thyroid cartilage. Upper and Lower Airway Conditions like subglottic stenosis may manifest acutely or subacutely, leading to cough, voice changes, or breathlessness. Severe narrowing can result in stridor, requiring urgent medical attention to avoid mortality (Fig. 378-3A). Often misdiag nosed as adult-onset asthma, timely recognition of airway involvement is important to prevent chronic damage to the large airways, which can result in tracheomalacia, bronchomalacia, or tracheal calcification (Fig. 378-3B and C). Patients with intermittent episodes of wheezing A FIGURE 378-2 Nose involvement in relapsing polychondritis. A. Redness and swelling of the base and tip of the nose. B. Saddle nose deformity.

 and with a review of symptoms positive for possible RP should be fol lowed closely and further evaluated for lower airway involvement. Musculoskeletal • JOINTS RP is associated with a nonerosive inflammatory arthritis that can affect small and large peripheral joints and as well as the axial skeleton. Erosions have been described in the sacroiliac joints but not in other joints. The most common large joint affected is the knees, often presenting

with effusions. The pattern of small joint involvement emulates rheumatoid arthritis, without ero sions or deformities. TENOSYNOVITIS Different tendons can be affected including Achilles and peroneal tendons. COSTOCHONDRAL JOINTS Located at the rib-sternum junction, these joints are frequently inflamed in RP, producing constant pain that B

PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders A B C FIGURE 378-3 Airway involvement in relapsing polychondritis. A. Subglottic stenosis. B and C. Computed tomography demonstrating tracheal calcification and tracheomalacia.

stands out due to its unique severe quality. Pain due to costochondritis can be so severe that patients will seek evaluation in the emergency room due to concerns for an acute coronary event. The pain is bilateral, reproducible with palpation, and not associated with movement of the affected rib. Inner Ear All patients with RP should undergo hearing tests to evaluate for conductive and sensorineural hearing loss. During the physical exam, the ear canal should be evaluated as some patients can have severe inflammation or eustachian tube dysfunction leading to conductive hearing loss. The presence of dizziness necessitates further evaluation through maneuvers like finger-to-nose, Romberg, and nys tagmus to rule out vestibular involvement. Ocular Involvement Episcleritis is the most frequent type of ocu lar inflammation in RP. It might coincide with other flare symptoms or occur independently. Although rare, features suggesting scleritis man date urgent ophthalmologic evaluation due to its potential catastrophic outcomes, including vision loss, scleromalacia, or global rupture neces sitating enucleation (Fig. 378-5A). Cardiovascular Patients with mouth and genital ulcers with inflamed cartilage (MAGIC) syndrome may exhibit symptoms seen in Behçet’s syndrome (Chap. 376), including pathergy and gastrointes tinal involvement. These patients can also have large-vessel vasculitis involving the aorta. Neurologic The diagnosis of neurologic involvement due to RP is one of exclusion. All possible etiologies including infection and malig nancy should be ruled out before attributing the clinical findings to RP; however, encephalitis and meningitis can be seen in RP. ■ ■DIAGNOSIS There are no circulating or tissue-based biomarkers with adequate performance characteristics to function as a diagnostic test for RP. As such, diagnosis is based primarily on clinical pattern recognition informed by a comprehensive review of systems and physical examina tion. Several diagnostic criteria have been proposed; however, these criteria were developed in small cohorts, are largely based on expert opinion, and have not been formally validated. McAdam’s criteria require presence of three of six symptoms, including bilateral auricular chondritis, nonerosive seronegative inflammatory polyarthritis, nasal chondritis, ocular inflammation, respiratory tract chondritis, or ves tibular/cochlear dysfunction. Damiani and Levine modified McAdam’s criteria to include either three clinical features or one clinical feature with histologic evidence of chondritis or two clinical features with clinical response to glucocorticoids, dapsone, or both. Michet’s criteria propose three major criteria (inflammation of ear, nose, or respira tory tract) and four minor criteria (ocular inflammation, hearing loss, vestibular dysfunction, and seronegative inflammatory arthritis) and require fulfillment of two major criteria or one major plus two minor criteria to establish the diagnosis. Another important limitation of these criteria is the lack of precise definitions of organ involvement. The differential diagnosis for RP includes conditions that mimic chondritis in specific cartilaginous organs and systemic diseases for which chondritis may be a manifestation. Ear chondritis can be mim icked by infectious and cutaneous diseases of the external ear, trau matic otohematoma, or red ear syndrome. Various infectious diseases and angiocentric centrofacial lymphoma can mimic nasal chondritis. Asthma, traumatic airway stenosis, infectious diseases, and congenital disorders involving the airway can mimic airway chondritis. Systemic diseases that

mimic RP include GPA (Chap. 375) and autoinflamma tory diseases (Chap. 381). GPA can be differentiated from RP in part by the presence of antineutrophil cytoplasmic autoantibodies (ANCA) and glomerulonephritis, which are not features of RP. Presence of cytopenia, most notably macrocytosis and lymphopenia, in older male patients should trigger consideration of genetic testing and bone mar row assessment for VEXAS. Audiometry to assess hearing loss and dynamic expiratory phase computed tomography of the chest to assess tracheobronchomalacia are critical studies that should be performed in all patients with suspected

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