POLYMYOSITIS AND DERMATOMYOSITIS

Prevent pneumothorax recurrence. Several techniques have been developed to accomplish these objectives.

Open thoracotomy allows for the resection or stapling of apical blebs followed by a mechanical pleural abrasion or parietal pleurectomy to create a pleural symphysis and prevent pneumothorax recurrence. Pneumothorax recurrence rates are less than 1%. However, with the significant postoperative morbidity associated with an open thoracotomy, less invasive techniques have been developed.

The application of video-assisted thoracic surgery (VATS) allows for an endoscopic approach in the management of pneumothorax. This technique allows for the endoscopic stapling of apical blebs and partial pleurectomy. Pleurodesis can be accomplished by either pleural abrasion or insufflation of talc. VATS is an acceptable technique in preventing pneumothorax recurrence for patients with PSP and SSP. Currently, VATS is the surgical procedure of choice in the management of SSP. Although there is no current data to indicate that bullctomy must be performed when talc is administered by poudrage, less successful procedures may be performed in patients at prohibitive risk for general anesthesia. The timing for VATS in the management of pneumothorax remains a matter of debate. Most authors agree that pneumothorax prevention is cost justified in SSP after the first pneumothorax occurrence. However, patient preferences and underlying lung diseases will influence this recommendation. In the management of PSP, most experts recommend VATS only after ipsilateral recurrence.

Pleurodesis should not be withheld in patients who might need lung transplantation. Although surgery is technically more difficult after pleurodesis, the consequences of pneumothorax in this fragile subset of patients can be catastrophic. The time that is required from the pleurodesis procedure until an effective pleural symphysis has occurred remains unknown but is estimated at approximately 2 weeks. Therefore, the time from pneumothorax occurrence to safe resumption of air travel remains controversial and depends on whether pleurodesis was performed and type of lung disease. In general, individuals with previous pneumothoraces should be discouraged from diving.


Further Reading


POLYMYOSITIS AND DERMATOMYOSITIS

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Abstract

Polymyositis (PM) and dermatomyositis (DM) are idiopathic inflammatory myopathies of autoimmune origin involving the skeletal muscles. Pulmonary involvement occurs and is a source of morbidity and mortality. The main forms of pulmonary involvement include interstitial lung disease, respiratory muscle weakness, and aspiration pneumonia. Non-specific interstitial pneumonia, organizing pneumonia, usual interstitial pneumonia, diffuse alveolar damage, and lymphocytic interstitial pneumonia are the main histologic patterns found. Anti-Jo-1 antibody (anti-histidyl-tRNA synthetase) is commonly found
in patients with PM/DM-associated interstitial lung disease. Progressive interstitial lung disease and respiratory muscle weakness can both cause respiratory failure. Aspiration pneumonia is related to weakness of the pharyngeal and upper esophageal muscles. Uncommon pulmonary manifestations include pleural effusion and pleuritis, pulmonary hypertension, and vasculitis. Corticosteroid therapy is the first line treatment and is generally effective in controlling both the myositis and the pulmonary involvement. However, in some patients PM/DM deteriorates despite corticosteroids and immunosuppressive therapy. Better understanding of the pathogenetic mechanisms in PM/DM will lead to more specific, target-directed therapy.

Introduction

Idiopathic inflammatory myopathies represent a heterogeneous group of autoimmune syndromes involving the skeletal muscle. The common traits of these disorders include muscle weakness and inflammation. Three major forms of idiopathic inflammatory myopathy include polymyositis (PM), dermatomyositis (DM), and inclusion-body myositis. Each of these entities has distinctive clinical and histopathologic features but the cause remains unknown. Idiopathic inflammatory myopathies are associated with systemic complications including involvement of the lungs. Pulmonary complications in idiopathic inflammatory myopathies are common causes of morbidity and mortality. This article focuses on lung involvement that occurs in patients with PM and DM.

The prevalence of inflammatory myopathies has been estimated to range from 0.6 to 6 per 100,000 and estimated incidence has varied from 0.1 to 0.9 per 100,000 per year. There is meager data on the relative incidence of the different forms of inflammatory myopathies. DM may occur in children and adults, whereas PM occurs mainly after the second decade of life. Both DM and PM are more common in females. In all age groups, DM is more common than PM.

Etiology

The cause of PM/DM is unknown, but these diseases are likely multifactorial in origin involving both genetic predisposition and acquired factors. The role of genetic factors is suggested by occasional familial occurrences, a higher frequency of other autoimmune disorders in the first-degree relatives of these patients, and linkage to certain human leukocyte antigens (HLA). Multiple genes, for example, immune response genes, likely contribute to susceptibility to these disorders. Exposure to certain environmental toxins, drugs, or infectious agents may play a role in some cases. PM-like syndrome has been described in chronic graft-versus-host disease.

Diagnosis

The clinical diagnosis of PM and DM is confirmed by three tests: serum muscle enzyme level, electromyography, and muscle biopsy. The most sensitive muscle enzyme test is the serum creatine kinase (CK) level which is usually elevated in patients with active PM or DM, but may occasionally be normal. Electromyographic results are usually abnormal, but the findings are non-specific and may be patchy.

The definitive diagnosis of inflammatory myositis requires a muscle biopsy obtained for conventional light microscopic examination as well as immunohistochemical and electron microscopic studies. Pathologic features common to both disorders include necrosis as well as various stages of regeneration involving the muscle fibers. These changes are accompanied by inflammation involving predominantly mononuclear cells and an increased amount of connective tissue. However, there are some microscopic, immunohistochemical, and ultrastructural findings in the muscle biopsy that distinguish PM from DM. Magnetic resonance imaging or computed tomographic scanning can sometimes be helpful, for example, selecting an appropriate biopsy site, but their diagnostic accuracy has not been adequately evaluated.

The most common autoantibodies in PM/DM are antisynthetase antibodies directed against various aminoacyl t-RNA synthetases. The best-known antisynthetase antibody is anti-Jo-1 (anti-histidyl tRNA synthetase), which is the most common type detected in patients with PM/DM-associated interstitial lung disease (ILD). The diagnostic and prognostic value of anti-Jo-1 in patients with PM/DM has not been adequately evaluated. Serum level of KL-6, a mucin-like high-molecular-weight glycoprotein, tends to be elevated in patients with PM/DM-associated ILD and may be a useful marker for assessing the activity of ILD.

Pathogenesis

Pathogenesis of PM and DM likely involves autoimmune responses, but target antigens have not been identified. In DM, the primary target antigen may be the endothelium of the endomysial capillaries. A high percentage of CD4 T cells and B cells are seen in the perivascular inflammation. In PM, certain CD8 T cells are clonally expanded in the muscle, possibly driven by an autoantigen. The autoimmune nature of this process is suggested by the association with autoantibodies, other autoimmune disorders, histocompatibility genes, and various T-cell products. A variety of inflammatory chemokines and proinflammatory cytokines including interleukin (IL)-1, IL-2,
IL-6, IL-10, tumor necrosis factor alpha (TNF-α), and transforming growth factor beta have been described to be upregulated in PM and DM.

Although antisynthetase antibodies are more commonly found in patients with PM/DM-associated ILD compared to those without ILD, the pathogenesis of ILD in these patients remains unknown. The development of ILD in these patients does not appear to correlate with the extent and severity of the muscle or skin disease.

**Animal Models**

A completely satisfactory animal model of PM or DM has yet to be developed. Some animal models for PM have been produced experimentally in guinea pigs, rats, and mice by immunization with homogenates of muscle or muscle protein preparations such as skeletal myosin or C protein. This process has been shown to produce experimental autoimmune myositis with infiltration of T cells into muscle and appearance of necrotic as well as regenerating muscle fibers.

**Clinical Features**

**Muscle Weakness**

Patients with PM and DM usually present with varying degrees of muscle weakness that is progressive over several weeks to months. Muscle weakness tends to be more severe in the shoulder and pelvic girdle muscles resulting in difficulty performing certain tasks, such as rising from a chair, climbing stairs, or combing hair. Myalgias are relatively uncommon. As the disease advances, dysphagia and respiratory muscle weakness may occur, but sensation remains normal.

**Skin Involvement**

DM is recognized by the characteristic skin rash that often precedes muscle weakness. These skin manifestations include the heliotrope rash on the upper eyelids, Gottron rash on the knuckles, and an erythematous rash on the face, neck, and upper chest and shoulders (Shawl sign). In some patients, the skin rash may be the dominant manifestation and muscle strength may appear normal (amyopathic dermatomyositis). Subcutaneous calcinosis can occasionally be seen, particularly in juvenile DM, and may result in pain, ulcerations, and infections.

Other organs including the gastrointestinal tract, joints, heart, and lungs can be involved in patients with PM/DM. In addition, features of PM/DM can overlap with other autoimmune and connective tissue diseases in some patients.

**Lung Involvement in PM/DM**

The main forms of pulmonary involvement in PM/DM include ILD, respiratory muscle weakness, and aspiration pneumonia (Table 1). The reported prevalence of pulmonary involvement in PM/DM has varied from 5% to 80%, depending largely on the method of detection, the diagnostic criteria, and the study population. For example, the prevalence of ILD in retrospective studies has ranged from 5% to 9%. However, the use of high-resolution computed tomography (HRCT) in prospective surveys has yielded a prevalence as high as 80%. Women with PM/DM are at a higher risk of developing ILD and the mean age at presentation is 50 years. Less common respiratory manifestations of PM/DM include pulmonary hypertension, vasculitis, and pleural involvement.

The clinician needs to keep in mind that a respiratory problem occurring in a patient with a known systemic disease may not only be a manifestation related to the underlying disease, but could also be a complication resulting from treatment, or an unrelated separate disease process. A broad perspective needs to be maintained at the outset of this diagnostic evaluation. In those patients with suspected ILD, the clinician needs to consider the need for lung biopsy to identify the underlying histologic pattern. Assessment of the tempo of the pulmonary disease, radiologic pattern seen on HRCT, and the clinical context will be helpful in reaching this decision. For example, bronchoscopy with bronchoalveolar lavage may suffice if the main concern is possible opportunistic infection. On the other hand, distinguishing different forms of interstitial pneumonias that can occur in patients with PM/DM generally requires a surgical lung biopsy. In many cases, however, identifying the specific histologic pattern of interstitial pneumonia may not necessarily alter treatment decisions since corticosteroid therapy is usually

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<td>Interstitial lung disease</td>
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<td>Non-specific interstitial pneumonia</td>
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<td>Organizing pneumonia</td>
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<td>Usual interstitial pneumonia</td>
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the primary mode of treatment for patients with PM/DM.

**Interstitial Lung Disease**

ILD is probably the most common form of pulmonary involvement in PM/DM. ILD is more common in patients with detectable autoantibodies to tRNA synthetases or a mucin-like glycoprotein (KL-6) in the serum. In some patients the ILD precedes the muscle or skin manifestation. There appears to be no correlation between the extent and severity of the muscle or skin disease and the development of ILD. Typical presenting manifestations in patients with PM/DM-associated ILD include progressive exertional dyspnea, nonproductive cough, and bibasilar crackles. Occasionally, the respiratory symptoms may be abrupt in onset and severe, resembling acute respiratory distress syndrome. Digital clubbing is rare.

Anti-Jo-1 antibody (anti-histidyl-tRNA synthetase), the most common type of antisynthetase autoantibody in patients with PM/DM, is detected more commonly in patients with associated ILD (50–70%) than in those without (10–15%). Some patients may present with ILD associated with anti-Jo-1 antibody in the absence of muscle involvement.

In patients with PM/DM-associated ILD, the most common histologic pattern seen in the lung is non-specific interstitial pneumonia (NSIP). Histologic features of NSIP are characterized by a uniform-appearing, cellular interstitial pneumonia with a lymphoplasmacytic infiltrate within alveolar septa. Varying amounts of fibrosis are admixed with the chronic inflammation. In contrast to usual interstitial pneumonia (UIP), in NSIP, fibroblastic foci are rare and microscopic honeycombing is absent. The NSIP pattern of lung injury can be seen in patients with other connective tissue diseases as well as in many other clinical contexts. Less common forms of ILD seen in PM/DM include organizing pneumonia, UIP, diffuse alveolar damage (DAD), and lymphocytic interstitial pneumonia (LIP). Subclassification of ILD into these histologic patterns is valuable in predicting response to therapy and prognostication. Pulmonary vascular inflammation is uncommonly seen and includes cases of pulmonary capillaritis. Pleuritis is also relatively uncommon.

Chest radiography on patients with PM/DM-associated ILD usually reveals reduced lung volumes and bilateral interstitial opacities, more prominent in the lower lung fields. Consolidation is less commonly seen and honeycombing is unusual. Findings on HRCT will generally reflect the underlying histopathologic pattern of ILD. Main findings on HRCT for those patients with NSIP pattern are reticular and/or ground-glass opacities present bilaterally with or without consolidation (Figure 1). Traction bronchiectasis may also be present but honeycombing is usually absent. Patients with organizing pneumonia (Figure 2) or DAD (especially during organizing phase) will have predominantly consolidative opacities on HRCT. Those with the UIP pattern of lung injury will characteristically manifest subpleural peripheral reticular opacities with or without honeycombing. Lymphocytic interstitial pneumonia is characterized by poorly defined centrilobular nodules, ground-glass opacities, and scattered thin-walled cysts. Pleural effusions may be seen in up to 20% of patients with PM/DM-associated ILD and are generally small in size.
Pulmonary function testing in patients with PM/DM-associated ILD usually demonstrates restrictive abnormalities with reduced lung volumes and diffusing capacity as well as evidence of abnormal gas exchange.

Bronchoscopy is generally nondiagnostic in patients with PM/DM-associated ILD. Transbronchial biopsy may yield evidence of interstitial inflammation and fibrosis but is unlikely to characterize fully the underlying histologic pattern. Bronchoalveolar lavage generally demonstrates lymphocytosis in the bronchoalveolar lavage fluid for those with NSIP and organizing pneumonia but can yield variable findings in those patients with other histologic patterns.

**Respiratory Muscle Weakness**

Involvement of respiratory muscles by progressive inflammatory myopathy can result in hypoventilation and occasionally respiratory failure. Isolated diaphragmatic weakness without peripheral muscle involvement has been described as well. Rarely, laryngeal involvement may occur.

In patients with respiratory muscle weakness, chest radiography reveals reduced lung volumes with diaphragmatic elevation and discoid basilar atelectasis. Pulmonary function testing demonstrates changes of a restrictive abnormality with reduced maximal respiratory pressures.

**Aspiration Pneumonia**

Dysphagia and reflux resulting from myopathy of the striated muscles of the hypopharynx and upper esophagus can predispose to aspiration. Impaired cough from respiratory muscle weakness may contribute to increased risk of aspiration for patients with PM/DM. Aspiration pneumonia has been reported to occur in 15–20% of patients with PM/DM. The diagnosis of aspiration pneumonia is usually made based on the radiologic findings and the clinical context. Respiratory muscle weakness is usually suggested by clinical and radiographic findings. Reduced maximal respiratory pressures will confirm this diagnosis. Chest radiography and CT typically demonstrate patchy consolidation in the dependent portions of the lungs. Biopsy confirmation is sought only if presenting clinical or radiologic features are atypical.

**Other Respiratory Manifestations**

Several other respiratory manifestations have been associated with PM/DM. Pulmonary hypertension can rarely be a direct manifestation of PM/DM but is seen more commonly secondary to progressive ILD or chronic ventilatory insufficiency. Few cases of pulmonary vasculitis including pulmonary capillaritis with associated diffuse alveolar hemorrhage have been reported in patients with PM/DM. The use of immunosuppressive agents such as methotrexate and cyclophosphamide can be associated not only with opportunistic pneumonias but with drug-induced lung diseases. Pleural manifestations have included pleural effusions, pleuritis, and occasionally spontaneous pneumothorax. DM, more so than PM, can be associated with cancer including lung cancer.

**Current Therapy**

The goal of therapy in PM and DM is to improve muscle strength and to ameliorate extramuscular manifestations. There have been very few controlled clinical trials. The treatment of inflammatory myopathies remains largely empirical, using agents that are nonselective in their effects on the immune system. Prednisone is the first-line drug and early initiation of therapy leads to better outcome. The initial dose of prednisone is usually 1 mg kg⁻¹ day⁻¹ with slow tapering to an alternate-day dosing over the following several months. Approximately two-thirds of patients will demonstrate a response to initial corticosteroid therapy. Large doses of intravenous corticosteroids, for example, 0.5–1 g methylprednisolone or equivalent given daily for 3 days, have been used in the initial management of severe cases. Addition of another immunosuppressive drug is commonly needed for steroid-sparing effect or for additive therapeutic effects in controlling the myositis. Azathioprine (2–3 mg kg⁻¹ day⁻¹) or methotrexate (up to 25 mg weekly) are commonly used for this purpose. In patients with aggressive disease, a combination of prednisone and another immunosuppressive drug can be started from the outset. Other treatment options include cyclophosphamide, cyclosporine, chlorambucil, mycophenolate mofetil, leflunomide, tacrolimus, anti-TNF agents (etanercept, infliximab), immune modulators (eculizumab, rituximab), plasmapheresis, total lymphoid irradiation, intravenous immunoglobulins, and autologous hemopoietic stem cell transplantation. None of these treatment modalities has been adequately tested in controlled clinical trials. In addition, relative efficacy of these agents used alone or in various combinations has not been clarified. Each patient needs to be individually assessed in regard to presenting manifestations, comorbid factors, and potential risks associated with the use of these agents. Rehabilitative measures including a regular exercise program may help to prevent or reverse impaired muscle function.
and exercise tolerance. Better understanding of pathogenetic mechanisms will lead to more specific, target-directed therapy in the future.

Management of respiratory involvement in patients with PM/DM depends on the type of pulmonary complication, the activity of the underlying PM/DM, and comorbid factors. In many cases, treatment of PM/DM itself, as outlined above, is the most important component in managing the pulmonary complication. For example, treatment of ILD associated with PM/DM involves corticosteroid and immunosuppressive therapy used to treat the underlying disease. The most common regimens used in managing patients with PM/DM-associated ILD are prednisone alone or in combination with azathioprine. The improvement in response to treatment is seen over the course of 4–6 months. This response to treatment in patients with PM/DM-associated ILD partly depends on the histologic pattern of lung injury. Patients with NSIP, organizing pneumonia, or LIP respond better to corticosteroid therapy and have a more favorable prognosis compared to those with UIP. Those patients with the DAD pattern have the worst prognosis. Thus, subclassification of histologic findings in patients with PM/DM-associated ILD appears to be clinically useful in gauging expected response to treatment and prognosis.

The serum CK level usually parallels the disease activity in PM/DM and should be monitored at regular intervals. In addition, reliable functional measures of muscle strength and endurance can help monitor the activity of PM/DM and response to therapy. Pulmonary function studies, chest radiographs, and HRCT of the chest provide objective reassessment of pulmonary involvement in PM/DM.

Other management options to be considered for patients with PM/DM and pulmonary involvement include ventilatory support and lung transplantation. In patients with respiratory failure from severe ILD or respiratory muscle weakness, invasive or noninvasive ventilatory support may be needed to survive an episode of exacerbation in their disease. Lung transplantation may be an option for those patients with severe pulmonary fibrosis resulting from PM/DM-associated ILD, in the absence of significant comorbid factors that may contraindicate this procedure and if the underlying PM/DM is under control.

**Prognosis**

The 5-year survival rate after diagnosis for patients with PM/DM overall is approximately 80%. The most common causes of death in these patients are cancer and pulmonary complications. At least a third of the patients with PM/DM are left with mild to severe muscle weakness. Pulmonary causes of death in patients with PM/DM include progressive ILD, ventilatory failure due to respiratory muscle weakness, recurrent aspiration pneumonia, pneumonias related to immunosuppressive therapy, and occasionally progressive pulmonary hypertension. The natural history of untreated ILD in PM/DM is not entirely known, but 5-year survival rates have been reported to be 50–60% for patients with PM/DM-associated ILD. Incomplete resolution of pulmonary opacities with residual bibasilar linear opacities is commonly observed in these patients.

DM, more so than PM, is associated with an increased risk of cancer. This excess risk of cancer appears to be highest around the time of diagnosis. Malignancies of the lungs, ovaries, breasts, and stomach are reported most frequently.

**See also:** Interstitial Lung Disease: Cryptogenic Organizing Pneumonia. Pulmonary Effects of Systemic Disease. Pulmonary Fibrosis. Respiratory Muscles, Chest Wall, Diaphragm, and Other.

**Further Reading**


PRIMARY CILIARY DYSKINESIA

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Abstract

Primary ciliary dyskinesia (PCD) is caused by ultrastructural ciliary defects that lead to abnormal ciliary beating and, subsequently, mucociliary dysfunction. PCD presents clinically with bronchiectasis, sinusitis, and, in up to 50% of cases, situs inversus. The ultrastructural defects of cilia are diverse but include in many cases outer and/or inner dynein arms. Recent advances have shown that ciliary defects in the embryonic node during development are responsible for the random right–left axis determination in these patients. Genetic approaches have elucidated at least some of the heterogeneous molecular defects underlying PCD. This article summarizes the current knowledge about this disease with respect to clinical manifestations, laboratory diagnosis and pathogenesis, situs inversus, genetics, and therapeutic considerations.

A report of a patient with the seemingly disparate symptoms of bronchiectasis and situs inversus 100 years ago is likely the first account of primary ciliary dyskinesia (PCD). Kartagener refined the description of the syndrome to include chronic sinusitis. However, only approximately 30 years ago, Afzelius and co-workers identified absent axonemal dynein arms in motile cilia with the ‘9 + 2’ microtubular arrangement of the airway epithelium and in sperm flagella as the cellular defect leading to what had come to be known as Kartagener’s syndrome or immotile cilia syndrome. Recent studies have demonstrated considerable heterogeneity of dynein arm morphology at the ultrastructural level among patients with this syndrome. Moreover, half of patients with clinical symptoms and ciliary ultrastructural defects do not exhibit situs inversus. Thus, the term PCD is currently used to describe individuals with congenital abnormalities of cilia and flagella and the clinical symptoms of bronchiectasis and chronic sinusitis. Kartagener’s syndrome, which in addition to bronchiectasis and sinusitis includes situs inversus, is thus considered a subset of PCD.

The overall incidence of PCD is 1 in 20 000, with enrichment in certain populations. PCD is usually an autosomal recessive disorder, but unusual cases of PCD with apparent dominant or X-linked inheritance pattern have also been reported.

Clinical Manifestations

Many clinical features of PCD reflect abnormal ciliary beating leading to impaired mucociliary clearance. Symptoms of mucociliary dysfunction in the nose, sinuses, and middle ear are recurrent or persistent rhinitis, sinusitis, and otitis media. Chronic productive cough is the major symptom of mucociliary dysfunction in the lower airways, and this chronic bronchitis can lead to bronchiectasis. Neonatal respiratory problems, situs inversus, and male infertility, common in PCD, are most likely linked to ciliary or flagellar dysfunction.

Chronic nasal congestion is common and often present from early infancy, with little or no seasonal variation. Almost all PCD patients have chronic sinusitis, radiographically demonstrated by mucosal thickening, cloudiness, and/or opacification of all paranasal sinuses. Nasal polyps occur in approximately one-third of patients and may be apparent in early childhood. Almost all patients have chronic otitis media that is much more prominent in early childhood. At the time of diagnosis, most patients