

## INTERSTITIAL LUNG DISEASES: ALGORITHM, TREATMENT AND FOLLOW-UP

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**SUMMARY** – Interstitial lung diseases and related difficulties that a clinician encounters in daily practice are presented. The disease may be of known origin, such as postirradiation pneumonitis, pneumoconioses, allergic alveolitis, etc., or of unascertainable origin, such as sarcoidosis and systemic diseases with multiple organ involvement, e.g., Goodpasture's syndrome. In the article, particular reference is made to sarcoidosis and cryptogenic fibrosing alveolitis. Interstitial diseases are still classified and referred to as (abbrev.) UIP, NSIP, DIP, LIP, BOOP and AIP. Both AIP and UIP are considered to have poor prognosis. This is a modification of Liebow's classification. The World Association of Sarcoidosis and Other Granulomatous Disorders has proposed guidelines for the follow-up of patients with these diseases. The recommended methods include bronchoalveolar lavage, angiotensin-converting enzyme determination, gallium scan (of the whole body or of the lungs), and high-resolution computed tomography. These parameters, along with clinical evaluation, and immunologic and functional tests, should prove adequate in most cases, while the rest of unresolved cases should be considered for either bronchoscopic transbronchial or surgical (thorascopic or open lung) biopsy. Most of our patients were treated with steroids, and only some 25% of them improved without this therapy. The patients treated with steroids responded to treatment without major side effects, with the exception of two patients who failed to respond favorably to this therapy. One of these two patients, however, had to be treated with low-dose steroids for more than ten years. New methods such as high-resolution computed tomography, along with the established ones such as gallium scan, help in the diagnosis of early stages of interstitial involvement, so that steroid therapy can be initiated on time, which is of crucial importance for prevention of the disease progression to the irreversible fibrotic stage. Prospective trials are needed to find new diagnostic and therapeutic methods based on novel concepts on the disease etiology.

*Key words: Lung diseases, interstitial, classification; Lung diseases, interstitial, diagnosis; Lung diseases, interstitial, therapy*

Differential diagnosis of diseases manifesting with proliferation of the pulmonary interstitium belongs to the most difficult fields not only in pulmonology but in general medicine as a whole. Normally, the interstitium should not be visible on a lung x-ray, and if seen, it points to pathologic changes due to viral or mycoplasma induced pneumonia. Cardiac decompensation, noncardiogenic

pulmonary edema (acute respiratory disease syndrome or acute pulmonary lesions) of unknown etiology (e.g., sarcoidosis), systemic disease with multiple organ involvement (e.g., Goodpasture's syndrome), miliary tuberculosis, occupational diseases (pneumoconioses, allergic alveolitis), or therapy induced alveolitis (e.g., Cordarone, bleomycin, TCT, actinotherapy) are states and syndromes that should be considered, recognized, properly treated, or possibly even prevented.

The interstitial pattern may be finely reticular, micronodular or macronodular, while in case of the alveolitis progression to fibrosis a frosted-glass shadow or honeycomb lung may develop.

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Cryptogenic fibrosing alveolitis or idiopathic pulmonary fibrosis is a disease of unknown etiology. A variety of criteria have been used for its classification, e.g., pathoanatomical, radiological, clinical, etc. According to recent concepts, there are pathologic changes of the interstitium as part of a syndrome, e.g., common interstitial pneumonia (UIP), desquamative interstitial pneumonia (DIP) or RBILD, acute interstitial pneumonia (AIP), nonspecific interstitial pneumonia (NSIP), giant cell interstitial pneumonia (GCIP) and lymphoid interstitial pneumonia (LIP), as modifications of the original classification according to Liebow.

The classification depends on the pathohistologic finding, while the material obtained by bronchoscopy and transbronchial biopsy may not always be representative enough for the cytologic or pathoanatomical diagnostic criteria. Therefore, attempts are made to reach an accurate diagnosis in an indirect and noninvasive way in order to initiate appropriate therapy on time, thus to prevent the progression of alveolitis to irreversible pulmonary fibrosis; and that is why the abbreviation for interstitial pulmonary fibrosis (IPF) should be distinguished from the abbreviation for interstitial lung disease (ILD).

Besides nonspecific symptoms, which need not always be present, the major symptom is shortness of breath on exertion, accompanied by dry cough (patients frequently describe inappetence, arthralgia and dry cough as a 'flu' or postvirolosis state). Hematologic, bacteriologic and serologic tests should be routinely performed. In case of multiple organ system involvement, functional tests of the liver, brain and kidneys, immunologic assays, and rheumatologic factor determination should also be performed. In case of interstitial pattern persisting after macrolide therapy, additional target testing should include respiratory function (restrictive ventilation impairment is frequently observed), supplemented by diffusion; gallium scintigraphy of the lungs or whole body; high-resolution computed tomography (CT); and bronchoalveolar lavage and/or transbronchial lung biopsy by bronchofibroscopy.

In addition to other parameters, mention should be made of the activity of the angiotensin converting enzyme (ACE), which is usually increased in sarcoidosis (stage 2) and points to granulomas still being formed in the lungs, indicating the activity of macrophages and T lymphocytes.

May all these parameters fail to result in timely and accurate diagnosis, while the disease continues to progress or no remission occurs, lung biopsy (open or during thoracoscopy) is performed in consultation with a thoracic surgeon and with patient's consent. This procedure pro-

vides an adequate, representative sample of the pulmonary tissue which will not reveal the etiology of disease, but will provide relevant information to justify the introduction of corticosteroid therapy (UIP and AIP have poorer prognosis than other interstitial diseases). The initial dose is 1 mg *per* kg body weight, and therapy should be administered for at least one year (except in case of negative finding of bronchoalveolar lavage in stage 1 sarcoidosis, i.e. in the stage of bihilar adenopathy, when spontaneous remission of the disease is expected to occur). Frequent controls, monitoring and management of side effects are necessary. In case of steroid intolerance or failure, alternative therapy includes cyclophosphamide, azathioprine, methotrexate, and colchicine, while the role of thalidomide and pentoxifylline is controversial. Before therapy introduction, gallium scintigraphy of the lungs or whole body and high-resolution CT should be performed to allow for subsequent follow-up of disease remission and assessment of therapeutic success.

Follow-up of the course of disease and treatment success includes lung x-ray, respiratory function assessment, and ACE determination at 1- to 2-month intervals in case of sarcoidosis. Bronchoalveolar lavage is not suitable for the purpose of follow-up. The criteria of severe alveolitis include lymphocyte predominance in bronchoalveolar lavage (cytology) and immunologic parameters, i.e. high percentage of T lymphocytes (>28%) and a T lymphocyte CD4:CD8 subpopulation ratio exceeding 3.5.

Sarcoidosis is a disease of unknown cause, with characteristic granuloma formation. Activated T lymphocytes and macrophages accumulate in granulomas, which may affect multiple organs (besides lungs and mediastinal lymph nodes, the liver, salivary glands, pericardium and central nervous system may also be involved). Unfortunately, specific antigens that trigger the cascade of immune events have not yet been identified. A combination of environmental effects and genetic predisposition leading to the multisystem disease has been speculated, however, from the view of a clinician there is no substantial difference in therapeutic approach in idiopathic pulmonary disease (alveolitis partially transforming to fibrosis) and stage 2 sarcoidosis.

High-resolution CT is of great value in detecting initial stage 2 disease that requires rapid diagnosis and therapy, because interstitial lesions can hardly be observed on lung x-ray, while regular CT cannot visualize granulomas in the stage of formation.

Among patients with sarcoidosis who had been regularly followed-up for several years, only three patients were

not prescribed corticosteroid therapy (initial stage of adenopathy, spontaneous disease regression). In the remaining patients, 12-month corticosteroid therapy proved efficacious, with uncomplicated course of disease and without major side effects. In two patients, the steroid dose had to be tapered at a faster rate due to adiposity and hypertension, which resulted in relapse of the disease necessitating dosage increase and prolonged therapy (18 months). In one patient, cyclophosphamide was introduced because of steroid therapy failure and intolerance. This secondary therapy was well tolerated by the patient and resulted in disease subsidence, however, at a somewhat slower rate. Two highly complicated cases included a patient with multisystem involvement (salivary glands, giving rise to suspicion of neurosarcoidosis). The dilemma has not yet been solved, and the patient has been submitted to additional studies. Steroid therapy was administered for about two years, and the patient reported polyarthralgias upon its discontinuation. In the other, female patient, therapy with low-dose steroid was prescribed for ten years because of multiorgan involvement, including the liver, eyes and pericardium. High-dose therapy was poorly tolerated by the patient, however, low-dose steroid therapy could not be discontinued because any attempt at corticosteroid administration only in the form of Becotide spray as a substitute for the maintenance dose failed.

Uncomplicated course of the disease was recorded in not more than some 25% of cases. We believe that control lung x-rays and ACE determination should be regularly performed at 1- to 2-month intervals in patients with verified sarcoidosis. Such a schedule should prove appropriate in patients with uncomplicated course of the disease. In case of poor therapeutic effect or failure (even with increased ACE without signs of lung disease exacerbation), gallium scintigraphy of the whole body should be performed at one-year intervals, whereas high-resolution CT should also be done at 6- to 12-month intervals in complicated cases. The follow-up of therapeutic success does not require bronchoalveolar lavage, as generally accepted worldwide.

It should be noted that a relatively small number of sarcoidosis patients were analyzed, thus the course of their disease could not be compared with other studies including more patients. Nevertheless, we may have declared some cases uncomplicated when other organs were also involved, or when stage 2 of the disease could not have yet been recognized, and gallium scintigraphy or high-resolution CT was not performed (discrepancy between a seemingly insignificant finding on lung x-ray, and gal-

lium scintigraphy or high-resolution CT is striking). Accordingly, none of the currently used methods can replace another one, but all these valuable methods should be considered complementary. Future prospective studies will hopefully result in novel concepts on these peculiar diseases that usually affect young people who develop acute states and syndromes which, if proceeding unrecognized, may even lead to lethal outcome unless the cascade of unfavorable events in the body being timely interrupted by appropriate therapy. The World Association of Sarcoidosis and Other Granulomatous Disorders has issued recommendations for the disease follow-up and assessment of the disease activity, which include serum ACE, high-resolution CT, gallium scintigraphy, and immunologic bronchoalveolar lavage parameters (listed above). We tried to use this follow-up algorithm even before we have learned about this consensus, reached in 1993.

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## Sažetak

## ALGORITAM PRETRAGA KOD BOLESTI PLUĆNOG INTERSTICIJA

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Prikazana je diferencijalna dijagnoza bolesti s patologijom intersticija, od bolesti poznatoga uzroka (karcinomatozna limfangioza, profesionalne bolesti, oštećenja pluća lijekovima ili zračenjem i druge) do bolesti nepoznatog uzroka (kriptogeni fibrozirajući alveolitis, sarkoidoza) i autoimunih bolesti sa zahvaćenjem više organa i pluća (Goodpastureov sindrom), koje predstavljaju dijagnostički problem. Intersticijske bolesti mogu biti izražene i u bolesti sa zahvaćenjem drugih organa (poznatog uzroka), npr. bubrega, jetre i srca. Upalne (virusne infekcije i infekcije mikoplazmom) i nasljedne bolesti također su spomenute. Posebna je pozornost posvećena kriptogenom fibrozirajućem alveolitisu i sarkoidozi, gdje uz rutinsku obradu treba provesti i dodatne pretrage angiotenzin konvertaze, plućne funkcije s difuzijom, dok rendgenske pretrage valja dopuniti kompjutoriziranom tomografijom visoke rezolucije. Često je potrebno provesti i scintigrafiju pluća (ili cijelog tijela) galijem, a od invazivnih pretraga treba provesti bronhoskopiju s transbronhijalnom biopsijom ili bronhoalveolarnu lavažu s citološkom i imunološkom analizom bronhoalveolarne lavaže (znakoviti omjeri subpopulacija T limfocita pokazuju radi li se o težem obliku alveolitisa). Ako ni nakon svih ovih pretraga nije jasno o kojoj se bolesti radi, u dogovoru s kirurzima izvodi se biopsija pluća (torakoskopska ili otvorena). Terapija kortikosteroidima nije bila potrebna u samo 25% bolesnika sa sarkoidozom, što se donekle razlikuje od podataka iz drugih klinika gdje je bio obuhvaćen veći broj bolesnika. Većina je bolesnika uza steroidnu terapiju ipak pokazala povoljan tijek, u dva od ukupno trinaest slučajeva komplikacije su bile jače izražene, dok jedna bolesnica od to dvoje mora trajno već preko deset godina uzimati kortikosteroide. U skladu s preporukama Svjetskog udruženja za sarkoidozu i granulomatoze treba, dakle, u početku bolesti učiniti (i) bronhoalveolarnu lavažu koja, međutim, nije pogodna za praćenje terapijskog učinka. Kontrolni su pregledi potrebni u određenim vremenskim razmacima. Uz angiotenzin konvertazu, treba provesti kontrolne pretrage kompjutoriziranom tomografijom visoke rezolucije, scintigrafiju toraksa i cijelog tijela galijem (po potrebi u vremenu kraćem od šest mjeseci), imajući pritom u vidu i cijene navedenih pretraga. Ovaj je algoritam na našoj Klinici primjenjivan i prije preporuka donesenih 1993. i 1994. godine. Potrebna su daljnja istraživanja, kao i praćenje ovih bolesnika, jer se radi o bolesti koja pogađa mlade ljude (prosječna dob u naših bolesnika bila je 30 godina), a kad se ne liječi, bolest prelazi u ireverzibilnu fibrozu. Kompjutorska tomografija visoke rezolucije i scintigrafija galijem poglavito su pogodne metode za dijagnosticiranje i praćenje bolesti intersticija, jer se na rendgenskoj snimci pluća ne vidi intersticij u ranoj fazi (mrežolik), dok obična kompjutorska tomografija ne razaznaje granulome u fazi njihova stvaranja.

*Ključne riječi: Plućne bolesti, intersticijske, klasifikacija; Plućne bolesti, intersticijske, dijagnostika; Plućne bolesti, intersticijske, terapija*