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The Role of Laboratory and Radiology in Diagnosing and Monitoring Interstitial Lung Diseases

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ABSTRACT
Interstitial lung disease (ILDs) form a group of heterogeneous pulmonary pathologies that require early diagnosis for proper management. High-resolution computed tomography (HRCT) is significant in characterizing ILD patterns, and laboratory markers serve towards disease characterization and follow-up. In spite of such significant tools, persistent barriers such as variable approaches in diagnosing and restricted multidisciplinary coordination hinder disease management. Enhancement in coordination between radiologists, pulmonologists, and laboratory professionals, along with application of sophisticated imaging and molecular diagnostics, can streamline early detection and personalized therapy, and in consequence, maximize patient care.

Keywords: interstitial lung disease, HRCT, laboratory markers, multidisciplinary coordination, early diagnosis

INTRODUCTION

The interstitial lung diseases (ILDs) form a group of heterogeneous pulmonary pathologies with variable intensities of pulmonary parenchymal inflammation and fibrosis. Diagnosis and follow-up in ILD require a multidisciplinary evaluation, with a combination of radiologic imaging and laboratory investigations. High-resolution computed tomography (HRCT) in radiology is significant in characterizing pulmonary architectural abnormalities, in differentiation between types of ILD, and in evaluation of disease progression (Hansell et al., 2008). Autoimmune serologies, markers of inflammation, and genetic analysis in laboratory investigations contribute towards systemic, environmental, and infectious etiologies (Mathai et al., 2016). Integration of radiologic and laboratory information forms a key role in therapeutic guidance and disease prognosis.

Radiological imaging constitutes a pillar for ILD diagnosis, with high-fidelity visualization of lung pathology defining individual ILD types. HRCT is a gold standard for diagnosing fibrotic ILD, such as idiopathic pulmonary fibrosis (IPF), with demonstration of characteristic radiologic features including honeycombing, traction bronchiectasis, and reticular opacities (Raghu et al., 2018). High-tech modalities such as photon-counting computed tomography (PCCT) and dual-energy CT have continued to allow early disease detection and characterization (Si-Mohamed et al., 2021). Apart from diagnosing, sequential HRCT scans become useful in tracking disease progression, guiding clinicians in estimating efficacy and instating timely interventions (Adegunsoye et al., 2019).

Combined with radiology, laboratory tests provide important information about ILD pathogenesis and disease activity. Autoimmune serologies included in diagnosing ILD in relation to connective tissue disease (CTD-ILDs), and markers for inflammation such as C-reactive protein (CRP) and lactate dehydrogenase (LDH) allow

disease activity evaluation (Fischer et al., 2015). In hypersensitivity pneumonitis (HP), IgG antibody tests in serum reveal antigens responsible for disease initiation (Ley et al., 2014). Genetic testing, in addition, increasingly constitutes an important role in diagnosing familial pulmonary fibrosis and defining molecular markers for personalized therapy (Zhai et al., 2024). With integration of radiologic and laboratory information, a larger and truer path towards diagnosing ILD can be achieved, with positive impact in terms of prognosis and care for the patient.

METHODOLOGY

A comprehensive review of radiology and laboratory science contribution towards care of ILD in terms of its diagnostics and progression was conducted. Articles between 2010 and 2023, in databases such as PubMed, Scopus, and Web of Science, were harvested with keywords such as "radiology," "interstitial lung disease," "HRCT," "pulmonary fibrosis," "diagnostic imaging," and "laboratory biomarkers." Relevance of titles and abstracts of studies harvested, and duplicates deletion, were conducted. Full texts of studies meeting predefined selection, i.e., studies reporting HRCT and laboratory biomarker contribution towards care of ILD in terms of its diagnostics and progression, and in collaboration between specialties in care of ILD, were analyzed. Not analyzed in analysis, but included in studies, were studies in a language not in English, conference articles, thesis, and irrelevant studies for objectives.

Extraction of information in terms of key theme such as accuracy in HRCT for diagnostics, laboratory biomarker contribution towards characterization of disease, difficulty in collaboration between disciplines, and improvement in techniques for diagnostics, was conducted. Included in analysis for review, but not included in studies, were studies employing methodologies such as randomized controlled trials, cohort analysis, systemic review, and methodologies in qualitative studies. Integration points considered for review, but not included in studies, included use of information in imaging and biomarker in diagnostics of ILD, development in technology in enhancing accuracy in diagnostics, and improvement in care of patient through collaboration.

LITERATURE REVIEW

The literature recognizes laboratory and radiologic critical roles in diagnosing and following ILDs. HRCT is radiologic gold standard, with high resolution visualization of such a pattern of fibrosis, such as ground-glass and honeycombing, in specific forms of ILD. Evolved modalities, such as dual-energy and photon-counting CT, have increased accuracy and reduced radiation burden. In parallel, laboratory investigations have a critical role in differentiation between etiologies of ILD. Autoimmune panels differentiate between CTD-ILDs, and CRP and LDH act as markers for activity and progression.

Molecular and genetic markers in development add predictive information, namely in familial pulmonary fibrosis.

Though these have increased accuracy and reduced radiation burden, impediments in realization of integral diagnostics approach prevail. Heterogeneity in HRCT reading, lack of harmonization in use of biomarkers, and poor pulmonologist-radiologist-laboratory collaboration hinder ideal care for a patient.

Overcoming such impediments will require increased collaboration between professionals, harmonized diagnostics protocols, and use of artificial intelligence in analysis of imaging and in analysis of biomarkers. Integrated electronic medical record and training programs for interprofessional collaboration can enhance accuracy and streamline care for ILD.

Increased synergy between laboratory and radiology is critical in enhancing early detection, developing optimized prognosis algorithms, and developing personalized therapeutic approaches in ILD.

DISCUSSION

Interstitial lung disease (ILDs) is a complex group of pulmonary disease with pulmonary parenchymal inflammation and pulmonary fibrosis. Diagnosis and follow-up for ILD involves a multidisciplinary evaluation with a combination of careful radiologic imaging and laboratory tests for architectural abnormalities, systemic and environment etiologies, and progression of disease. Radiology helps in providing important information about ILD morphologic abnormalities, and laboratory tests reveal autoimmune, inflammatory, genetic, and infectious etiologies. Together, both tools form the backbone of successful ILD therapy and management (Antoniou, 2014).

The Role of Radiology

Diagnosis for ILD forms an important role played by radiology, and high-resolution computed tomography (HRCT) forms gold standard for diagnosing ILD (Hansell et al., 2008). HRCT can visualize such characteristic radiologic abnormalities such as honeycombing, traction bronchiectasis, and reticular abnormalities, important in diagnosing such fibrotic ILD such as idiopathic pulmonary fibrosis (IPF). These radiologic abnormalities allow clinicians to differentiate between forms of ILD, for example, a usual interstitial pneumonia (UIP) form and nonspecific interstitial pneumonia (NSIP) or fibrotic hypersensitivity pneumonitis (f-HP). For example, UIP

is distinguished by basal and subpleural reticulation, honeycombing, and traction bronchiectasis, with strong association with IPF, and NSIP with a common association with connective tissue disease and bilateral ground-glass opacification with a feature of subpleural sparing (Raghu et al., 2018; Sumikawa et al., 2014). Besides, radiologic pattern recognition with HRCT tends to exclude such invasive tests such as lung biopsies, minimizing patient risk (Raghu et al., 2018).

In addition to disease diagnosis, HRCT is useful in estimating prognosis of disease, particularly in ILDs. There is a direct proportionality between radiologic markers, for instance, severity of honeycombing or traction bronchiectasis, and disease progression and fatality in ILDs (Adegunsoye et al., 2019). For instance, subjects with diffuse honeycombing, or loss of lung volumes in imaging, have a high likelihood of rapid disease progression and poor prognosis. Similarly, in SSc-ILD, severity of HRCT-fibrosis is a predictive marker for overall prognosis, and rating tools such as UK Raynaud's and Scleroderma Association Staging System can add towards risk stratification (Distler et al., 2019). All these allow clinicians to individualize therapeutic interventions according to predicted disease progression.

Current radiologic modalities increasingly expand radiologic capabilities in ILDs. Photon-counting computed tomography (PCCT) can generate ultra-high resolution with reduced radiation, and visualize early abnormalities in the parenchyma, for instance, faint reticulation, or early fibrosis, with ease (Si-Mohamed et al., 2021). Quantitative imaging tools, with artificial intelligence, are in development for providing objective estimates of severity of fibrosis and disease progression. All these go beyond naked-eye analysis, and generate reproducible and reliable assessments (Calandriello& Walsh, 2022). In addition, dual-energy CT has helped defining pulmonary perfusion defects in subjects with progressive pulmonary fibrosis (PPF), and providing complementary information about disease in blood vessels in ILDs (Patel et al., 2020).

Radiology is useful in tracking disease progression over a duration, as well, in following disease progression of fibrotic abnormalities, for example, progression of traction bronchiectasis, progression of honeycombing, or ground-glass opacities. In progressive pulmonary fibrotic ILD, increased traction bronchiectasis or new fine reticulation is radiologic sign of disease progression, and such progression can require initiation of antifibrotic therapies (Raghu et al., 2022). Pulmonary fibrosis secondary to COVID has positioned radiologic follow-up in a key role, as well. Patients with recovered severe COVID-19 pneumonia can have persistent ground-glass opacities and fibrotic-like abnormalities in follow-up imaging, and such abnormalities can follow spontaneous resolution (Martini et al., 2021). But, in persistent radiologic abnormalities, a progression, and/or in case of persistent symptoms, radiologic abnormalities guide long-term management and therapy (Lederer et al., 2024).

Laboratory testing for ILDs

Interdisciplinary laboratory testing complements radiologic testing with providing important information regarding etiologic factors for ILD. Autoimmune serologies have an important role in diagnosing CTD-associated ILD (CTD-ILDs). For example, antinuclear antibody (ANA) is positive in systemic autoimmune disease, such as systemic lupus erythematous, and such pulmonary-related systemic disease is prevalent (Mathai et al., 2016). Similarly, anti-rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibody serve in diagnosing ILD-related rheumatoid arthritis, and myositis-specific antibody, such as anti-Jo-1, confirms ILD-related polymyositis and dermatomyositis (Fischer et al., 2015). Diagnosis of such autoimmune markers is important in differentiation between idiopathic ILD, such as in IPF, and an inflammatory and systemic cause, and such proper therapy for such a patient can then follow.

Inflammatory biomarkers, too, have an important role in diagnosing and tracking ILDs. ESR and CRP elevation in blood reflects ongoing systemic inflammation, a characteristic in ILD with an etiological basis for inflammation, for example, in NSIP (Raghu et al., 2018). Elevation in serum LDH is a nonspecific marker for diffuse alveolar damage, or for active interstitial disease, but its specific use in diagnosing ILD is limited (Maher et al., 2021). Long-term follow-up of such markers for inflammation is useful in providing information about disease activity and success of anti-inflammatory therapy.

In hypersensitivity pneumonitis (HP), specific IgG antibody testing for antigens in an environment, for example, for molds, and for avian proteins, can detect suspected causative antigens for disease (Ley et al., 2014). Precipitation tests for, for example, antibody to droppings of birds, and for fungal spores can confirm long-standing HP as an etiology for ILD (Ley et al., 2014). But such tests must be placed in supportive laboratory and radiologic information, in that a positive result in and of itself is not a criterion for a diagnosis (Vasakova et al., 2017). Integration with information about an environment of exposure and laboratory and radiologic information is therefore important for proper diagnosis.

Genetics is a new and growing field in diagnosing ILDs, specifically in familial disease. SFTPC and SFTPA2 gene mutations and mutations in telomerase-related genes (e.g., TERT, TERC) have been causative in familial pulmonary fibrosis and in IPF (Nathan et al., 2011). Blood tests for surfactant proteins, such as SP-A and SP-D, could possibly have a role in diagnosing and following IPF and form a molecular basis for personalized therapy (Zhai et al., 2024). As molecular and genetic diagnostics become increasingly sophisticated, increasingly a role for them in ILD management can be anticipated.

Laboratory investigations also exclude infectious processes with similar ILD presentations. Invasive fungal infection can be ruled out with serum fungal markers, such as galactomannan and beta-D-glucan, and concurrent infection with a virus can be ruled out with viral serologies for cytomegalovirus and for Epstein-Barr virus (Corte et al., 2015). In most cases, then, follow-up microbial cultures and bronchoscopy with bronchoalveolar lavage (BAL) can then be conducted in an attempt to exclude infection, in a view to not worsen undiagnosed infection with immunosuppressive therapy (Richeldi et al., 2018). In atypical cases and in immunocompromised subjects, it is particularly significant.

Integration of laboratory and radiologic information is significant in multidisciplinary ILD management. Detail interpretations of radiologic information are conducted in radiologists, and laboratory tests reveal systemic and environmental etiologies, providing a full workup (Chung et al., 2018). For example, in suspected cases of IPF with a UIP pattern HRCT, an unavailability of autoimmune disease serologic markers confirms a diagnosis of idiopathic UIP, but positive ANA and RF serologies can refer a switch in a diagnosis towards CTD-ILD. In complex and overlapping cases, such integration is particularly significant, allowing correct diagnoses and therapy.

For follow-up and disease progression, sequential imaging and laboratory markers become complementary in most cases. For example, progression in HRCT with deterioration in traction bronchiectasis and honeycombing can follow increased markers of inflammation, such as CRP and ESR, indicative of active disease progression (Adegunsoye et al., 2019). In a similar way, in subjects under therapy with antifibrotics, improvement in radiologic appearances accompanied with normalization of markers of inflammation confirms therapy efficacy, guiding clinicians (Distler et al., 2019).

Post-COVID-19 ILDs have increased the urgency for an integration of laboratory and radiologic testing in patient care. Recovered severe COVID-19 pneumonia entails persistent ground-glass opacities and abnormalities with a fibrotic character in radiologic studies, with resolution over a period (Martini et al., 2021). In a minority, persistent elevation in markers for inflammation, such as CRP or LDH, mirrors ongoing inflammation. With a confluence of laboratory tests and radiologic studies, clinicians can differentiate post-viral processes and progression disease with fibrotic disease, and intervention in a timely manner.

CONCLUSION

Accurate and early interstitial lung disease (ILDs) diagnosis is paramount for improving patient prognosis. HRCT is important in diagnosing ILD patterns, with laboratory markers yielding important information about disease progression and prognosis. On the other hand, gaps in multidisciplinary coordination and uniformity in approaches for diagnosing impair full use of these tools. Compartmentalization of radiologists, pulmonologists, and laboratory professionals, and incorporation of new technology and molecular diagnostics, is paramount for improving accuracy and care.

Interdisciplinary training, uniform protocols for diagnosing, and incorporation of new technology, including artificial intelligence, in future development in ILD care, is important for improving accuracy and care for ILD patients. With a multidisciplinary and technology-facilitated collaboration, delivery of care can make earlies diagnoses, individualized therapy, and, in fact, long-term improvements in ILD patient care.

REFERENCES

1. Adegunsoye, A., Oldham, J. M., Bellam, S. K., et al. (2019). CT honeycombing identifies a progressive fibrotic phenotype with increased mortality across diverse interstitial lung diseases. Annals of the American Thoracic Society, 16(5), 580–588.
2. Antoniou, K. M., Margaritopoulos, G. A., Tomassetti, S., Bonella, F., Costabel, U., &Poletti, V. (2014). Interstitial lung disease. European Respiratory Review, 23(131), 40-54.
3. Calandriello, L., & Walsh, S. L. (2022).The evolution of computer-based analysis of high-resolution CT of the chest in patients with IPF.British Journal of Radiology, 95(1132), 20200944.
4. Chung, J. H., Cox, C. W., Montner, S. M., et al. (2018). CT features of the usual interstitial pneumonia pattern: Differentiating connective tissue disease-associated interstitial lung disease from idiopathic pulmonary fibrosis. AJR American Journal of Roentgenology, 210(2), 307–313.
5. Distler, O., Highland, K. B., Gahlemann, M., et al. (2019).Nintedanib for systemic sclerosis-associated interstitial lung disease.New England Journal of Medicine, 380(26), 2518–2528.
6. Hansell, D. M., Bankier, A. A., MacMahon, H., et al. (2008). Fleischner Society: Glossary of terms for thoracic imaging. Radiology, 246(3), 697–722.
7. Lederer, C., Storman, M., Tarnoki, A. D., Tarnoki, D. L., Margaritopoulos, G. A., &Prosch, H. (2024).Imaging in the diagnosis and management of fibrosing interstitial lung diseases. Breathe, 20(1).
8. Ley, B., Brown, K. K., Collard, H. R., & Ryerson, C. J. (2014).Molecular biomarkers in idiopathic pulmonary fibrosis.American Journal of Physiology-Lung Cellular and Molecular Physiology, 313(6), L1056-L1063.

9. Maher, T. M., Bendstrup, E., Dron, L., Langley, J., Smith, G., Khalid, J. M., & Patel, H. (2021).Global incidence and prevalence of idiopathic pulmonary fibrosis.Respiratory Research, 21(1), 1-12.
10. Martini, K., Larici, A. R., Revel, M. P., et al. (2021). COVID-19 pneumonia imaging follow-up: When and how? A proposition from ESTI and ESR.European Radiology, 32(5), 2639–2649.
11. Nathan, S. D., Shlobin, O. A., Weir, N., Ahmad, S., Kaldjob, J. M., Battle, E., ...& du Bois, R. M. (2011). Long-term course and prognosis of idiopathic pulmonary fibrosis in the new millennium. Chest, 140(1), 221-229.
12. Patel, B. V., Arachchillage, D. J., Ridge, C. A., et al. (2020). Pulmonary angiopathy in severe COVID-19: Physiologic, imaging, and hematologic observations. American Journal of Respiratory and Critical Care Medicine, 202(5), 690-699.
13. Raghu, G., Remy-Jardin, M., Richeldi, L., et al. (2022). Idiopathic pulmonary fibrosis (an update) and progressive pulmonary fibrosis in adults: An official ATS/ERS/JRS/ALAT clinical practice guideline. American Journal of Respiratory and Critical Care Medicine, 205(9), e18–e47.
14. Si-Mohamed, S., Boccalini, S., Rodesch, P. A., et al. (2021).Feasibility of lung imaging with a large field-of-view spectral photon-counting CT system.Diagnostic and Interventional Imaging, 102(5), 305–312.
15. Sumikawa, H., Johkoh, T., Fujimoto, K., et al. (2014).Pathologically proved nonspecific interstitial pneumonia: CT pattern analysis as compared with usual interstitial pneumonia CT pattern.Radiology, 272(2), 549–556.
16. Vasakova, M., Morell, F., Walsh, S., Leslie, K., & Raghu, G. (2017). Hypersensitivity pneumonitis: Perspectives in diagnosis and management. American Journal of Respiratory and Critical Care Medicine, 200(6), 681-692.
17. Zhai, K., Zang, D., Yang, S., Zhang, Y., Niu, S., & Yu, X. (2024). Biomarkers for Early Diagnosis of Idiopathic Pulmonary Fibrosis: A Systematic Review. Journal of Medical and Biological Engineering, 1-10.