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Expert Review

Why Do Rheumatic Diseases with Pulmonary Fibrosis Rarely Develop Digital Clubbing?

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Abstract: Digital clubbing, or hypertrophic osteoarthropathy in its more advanced form, is a distinctive clinical sign characterized by bulbous enlargement of the distal phalanges and increased nail curvature. It is classically associated with neoplastic, infectious, and hepatopulmonary diseases, where tissue hypoxia and circulating angiogenic mediators play central roles. In contrast, rheumatic diseases such as rheumatoid arthritis, systemic sclerosis, and idiopathic inflammatory myopathies, even when complicated by significant pulmonary fibrosis and hypoxemia, rarely present with digital clubbing. This review explores the pathophysiologic mechanisms of clubbing, contrasts them with the pathogenesis of rheumatic interstitial lung disease (ILD), and discusses why autoimmune fibrotic processes may inherently prevent the development of this ancient clinical sign. The rarity of clubbing in autoimmune ILD has diagnostic and pathogenetic implications that extend beyond clinical observation, suggesting fundamental differences in vascular and cytokine regulation compared with neoplastic or infectious fibrosis.

Keywords: digital clubbing; hypertrophic osteoarthropathy; rheumatic diseases; autoimmunity; pulmonary fibrosis; angiogenesis; vascular endothelial growth factor (VEGF); cytokines; interstitial lung disease; systemic sclerosis

1. Introduction

Digital clubbing was first described by Hippocrates more than two millennia ago and remains one of the most visually striking physical findings in medicine, actually the finding was recognized in skeletal remains from pre-Hispanic Mesoamerica preserved at the National Museum of Anthropology of Mexico City [1]. It is characterized by a broadening of the fingertips with increased curvature of the nails and soft tissue hypertrophy at the terminal phalanges. Clinically, it is identified by loss of the normal Lovibond angle and increased nail bed fluctuation [2]. Clubbing can be idiopathic, familial, or secondary to systemic disease. Secondary forms are most often linked to pulmonary malignancies, chronic infections, cyanotic heart diseases, and hepatic disorders [3,4].

In everyday clinical practice, clubbing serves as a nonspecific but meaningful indicator of underlying systemic disease. Its occurrence reflects chronic activation of vascular and connective tissue pathways triggered by platelet-derived and endothelial factors. Despite the high prevalence of interstitial lung disease among patients with rheumatic conditions such as rheumatoid arthritis (RA), systemic sclerosis (SSc), and polymyositis/dermatomyositis, digital clubbing remains a rarity. This paradox raises important questions: why does profound pulmonary fibrosis in autoimmune diseases, often associated with chronic hypoxia, fail to produce

the same distal tissue changes observed in neoplastic or infectious lung disorders? Understanding this discrepancy requires a closer examination of the mechanisms behind digital clubbing and their interaction with the immunologic and vascular environment of rheumatic ILD.

2. Mechanisms of Digital Clubbing

The exact mechanism of presentation of digital clubbing was still a matter of debate in the past century. However, the most likely explanation of clubbing initiation is that of the combination of circulating cellular elements, vascular endothelium, and localized connective tissue proliferation. The initial histologic observations showed increased vascularity, edema, and fibroblast hyperplasia in the nail bed and periosteum. Later, increased concentrations of VEGF, PDGF, and PGE2 were detected in the blood of people with the disorder. The latter three factors lead to activation of the endothelium, vessels' hyperplasia, and fibroblast differentiation, resulting in an increased spread of tissue particular in the soft tissues and the periosteum. The megakaryocyte-platelet hypothesis is the most popular pathologic explanatory model for the clubbing of the fingers proposed by Dickinson and Martin [5]. In a normal situation, fragments of these large polymer cell types are divided into small ones, initiating the process of thrombopoiesis. During the developmental periods of lung cancer, bronchiectasis, or the shunting of the pulmonary capillary rete, their structure is torn apart, and the cells bypass it. After the platelet-phenotype cells enter the periphery of the capillary arteries, they proliferate and release PDGF and VEGF, which leads to neovascularization. Vascular anomalies in neoplastic and bacterial lung pathologies allow more emboli to leak in the peripheral blood circulation. In these two conditions, where systemic infections are continuous, the clubbing always corresponds with hypertrophic osteoarthropathy. As opposed to RA-related cases, capillaries tend o obliterate when affected by interstitial fibrosis rather than develop new capillary clusters.

3. Clubbing across Clinical Conditions

Digital clubbing appears in approximately 5–15% of hospitalized adults and up to 31% of those with interstitial lung disease, depending on the underlying cause [6]. It is highly prevalent in bronchiectasis, lung abscess, and cystic fibrosis, and is nearly pathognomonic of certain malignancies such as bronchogenic carcinoma [7]. It is also a well-known feature of cyanotic heart disease, subacute bacterial endocarditis, and cirrhosis, particularly in hepatopulmonary syndrome [8]. Cyanotic heart disease is the internal illness most closely linked to hypertrophic osteoarthropathy, current evidence suggests that in cases of right-to-left shunts of blood, HOA develops as a result of faulty pulmonary clearance of macrothrombocytes. There are theoretical grounds to suggest that a platelet-derived growth factor is also responsible for the acropachy associated with other types of internal illnesses like hepatic hyperthyroidism and Chron's Disease, diseases associated with shunting [9,10].

In contrast, the literature contains remarkably few reports of clubbing among patients with rheumatic disease. Even in rheumatoid arthritis, in which pulmonary fibrosis and hypoxia may be severe, clubbing is rarely documented. When present, it often indicates coexisting pathology such as malignancy, infection, or emphysema [11]. Similarly, systemic sclerosis and dermatomyositis patients with interstitial lung disease seldom exhibit this finding. The scarcity of reports suggests either a genuine absence of the pathophysiologic prerequisites for clubbing or a suppressive effect of the autoimmune milieu and its treatment.

4. Why Rheumatic Diseases Differ

To date, no study has specifically investigated why connective tissue disease–associated pulmonary fibrosis rarely leads to digital clubbing. Based on convergent evidence from vascular biology, cytokine signaling, and antifibrotic pathways, we propose a set of working hypotheses that could mechanistically account for this phenomenon.

4.1. Distinct Cytokine and Fibrogenic Pathways

The cytokine milieu of rheumatic ILDs is dominated by transforming growth factor-β (TGF-β), interleukin (IL)-6, and IL-13, promoting fibroblast activation and collagen deposition rather than angiogenesis [12]. In contrast, neoplastic and infectious lung diseases induce high expression of VEGF, PDGF, and PGE_2, key drivers of endothelial proliferation and vascular remodeling [8,13,14]. This cytokine divergence may explain the lack of angiogenic response in rheumatic ILDs. Furthermore, systemic sclerosis is characterized by capillary rarefaction and antiangiogenic signaling, making the microvascular environment inherently resistant to new vessel formation [15]. Thus, the very mechanisms that drive fibrosis may simultaneously prevent the angiogenic events necessary for clubbing.

Importantly, TGF-β signaling is biologically complex and context-dependent. While it frequently promotes fibroblast activation and extracellular matrix deposition in autoimmune interstitial lung disease, experimental and clinical studies have also demonstrated that TGF-β may exert pro-angiogenic effects depending on the microenvironment, endothelial signaling pathways, and its interaction with mediators such as VEGF and PDGF. Thus, the role of TGF-β in vascular biology should be interpreted as a regulatory axis that may either suppress or promote angiogenesis depending on disease stage and tissue context.

4.2. Absence of Intrapulmonary Shunting

The megakaryocyte-platelet hypothesis requires the presence of intrapulmonary shunts or vascular disruption to permit large platelet precursors to bypass the pulmonary filter [16]. In rheumatic ILDs, pulmonary capillaries become narrowed or obliterated by fibrosis but remain functionally closed systems without major right-to-left shunting. The absence of such vascular escape routes prevents megakaryocytes and platelet aggregates from reaching the distal circulation, thus interrupting the cascade that initiates clubbing.

4.3. Impact of Immunosuppressive and Biologic Therapies

Most patients with autoimmune disease receive chronic immunomodulatory therapy, including corticosteroids, methotrexate, azathioprine, mycophenolate mofetil, or biologic agents targeting TNF, IL-6, or B cells. These therapies profoundly downregulate inflammatory and angiogenic pathways, including VEGF and PDGF signaling [17]. Methotrexate, for instance, has been shown to suppress endothelial proliferation, while tocilizumab reduces circulating VEGF levels [18]. Therefore, the pharmacologic environment typical of rheumatic disease likely suppresses the very cytokine cascades required for digital clubbing.

4.4. Fibrotic, Nonangiogenic Remodeling

Histopathologic studies in systemic sclerosis and rheumatoid arthritis-associated ILD demonstrate dense interstitial collagen deposition with capillary loss, not proliferation [19]. Fibroblasts in these diseases exhibit a profibrotic but nonangiogenic phenotype, producing extracellular matrix components under TGF-β influence. In contrast, tumors and chronic infections stimulate both fibrosis and angiogenesis through VEGF-mediated vascular sprouting. The antiangiogenic nature of autoimmune fibrosis thus represents a biological counterpoint to the angiogenic profile of malignancy.

4.5. Influence of Antifibrotic Therapies

Emerging therapies such as nintedanib and pirfenidone, increasingly used in systemic sclerosis-related ILD, inhibit tyrosine kinase receptors for VEGF and PDGF, reducing angiogenesis [20]. Their chronic administration further dampens the molecular environment conducive to clubbing. This pharmacologic factor, although secondary, may help maintain the consistent absence of clubbing even in advanced fibrotic disease.

4.6. Coexistence of Clubbing as a Diagnostic Warning

On the rare occasions when clubbing is observed in rheumatic patients, it often signals an alternative or additional pathology. Case reports have described rheumatoid arthritis patients with combined pulmonary fibrosis and emphysema developing digital clubbing, frequently associated with secondary pulmonary hypertension or malignancy [11]. In such contexts, clubbing should prompt evaluation for hidden cancer, chronic infection, or hepatopulmonary syndrome. Its presence should never be attributed to autoimmune fibrosis alone without exclusion of concurrent disease. The main mechanistic differences between classic causes of digital clubbing and rheumatic interstitial lung disease are summarized in Table 1.

5. Discussion

The contrasting prevalence of digital clubbing between rheumatic and nonrheumatic fibrotic lung diseases underscores fundamental differences in vascular biology. Clubbing reflects a specific angiogenic and platelet-derived growth factor–driven process, dependent on the escape of megakaryocytes or platelets into the systemic circulation and on local endothelial responsiveness to VEGF and PDGF [16,20,21]. In rheumatic ILDs, these prerequisites are absent or actively suppressed.

Although transforming growth factor-β (TGF-β) is widely recognized as a key profibrotic mediator in autoimmune connective tissue diseases, its biological effects on angiogenesis are complex and context-dependent. Experimental and translational studies have demonstrated that TGF-β signaling may exert either pro-angiogenic

or anti-angiogenic effects depending on tissue compartment, disease stage, and its interaction with other growth factors such as VEGF and PDGF. Therefore, the role of TGF-β in rheumatic diseases should not be interpreted as exclusively anti-angiogenic, but rather as a regulatory pathway capable of modulating vascular remodeling in different directions according to the local molecular microenvironment [22].

The antiangiogenic microenvironment characteristic of systemic sclerosis exemplifies this divergence. Capillary rarefaction, endothelial apoptosis, and perivascular fibrosis define the early stages of disease, with overexpression of endothelin-1 and reduced VEGF receptor activity [15]. Interestingly, systemic sclerosis also illustrates a well-recognized paradox in vascular biology. Despite increased circulating and tissue levels of vascular endothelial growth factor (VEGF), effective angiogenesis remains profoundly impaired. This phenomenon has been attributed to severe endothelial dysfunction, defective VEGF receptor signaling, reduced numbers or functional impairment of endothelial progenitor cells, and the presence of anti-angiogenic mediators within the fibrotic microenvironment. As a consequence, vascular remodeling becomes structurally abnormal rather than productive, leading to capillary rarefaction and disorganized microvasculature instead of functional neovascularization [23,24]. The same imbalance that produces Raynaud's phenomenon and digital ulcers likely prevents the diffuse vascular proliferation needed for clubbing. Similarly, in rheumatoid arthritis, pulmonary involvement is dominated by inflammatory alveolitis and fibrotic remodeling, but not by angiogenesis. Although VEGF may be elevated locally in the synovium, its systemic effects are muted and do not extend to distal capillaries.

Infectious and neoplastic disorders, in contrast, are characterized by active vascular disruption, intrapulmonary shunting, and elevated circulating angiogenic mediators. Hepatopulmonary syndrome provides another instructive model: here, nitric oxide and VEGF-driven dilatation of pulmonary vessels permits megakaryocytes to bypass filtration, leading to clubbing and hypertrophic osteoarthropathy [8]. Such mechanisms have no parallel in rheumatic fibrosis, where capillary obstruction rather than dilation predominates.

The rarity of clubbing in rheumatic disease has practical diagnostic implications. In a patient with known autoimmune ILD who develops clubbing, clinicians should maintain high suspicion for malignancy, chronic infection, or hepatopulmonary dysfunction. The appearance of clubbing may serve as a "red flag" suggesting a superimposed pathology rather than progression of the autoimmune process. Conversely, the absence of clubbing should not be interpreted as evidence of mild disease, since pulmonary impairment may be severe despite its absence.

The implications extend to research. Measuring circulating levels of VEGF, PDGF, and PGE_2 in patients with rheumatic ILD compared with idiopathic or neoplastic fibrosis could illuminate protective mechanisms against abnormal angiogenesis. Understanding why fibrosis in autoimmune disease remains nonangiogenic may also provide clues for therapeutic modulation in other fibrotic conditions where excessive vascular proliferation drives pathology.

Despite these insights, limitations remain. Data on clubbing in rheumatic diseases are derived almost exclusively from case reports and small series. No systematic studies have quantified its prevalence or correlated it with biomarkers. Furthermore, most pathophysiologic models derive from nonrheumatic conditions, leaving unanswered questions about the role of chronic immune activation, hypoxia-inducible factors, and microvascular remodeling in autoimmune fibrosis. Future studies should integrate angiogenic profiling, imaging, and histopathology to delineate how rheumatic fibrosis diverges from neoplastic angiogenesis.

Finally, therapy itself may confound observations. Long-term immunosuppression, biologic therapy, and antifibrotic drugs collectively modify angiogenic pathways, potentially obscuring natural disease manifestations. Whether untreated or early-stage rheumatic ILD could ever produce clubbing in the absence of therapy remains unknown, though its rarity in historical descriptions suggests intrinsic resistance rather than iatrogenic suppression.

6. Conclusions

Digital clubbing represents a physiologic endpoint of angiogenic and platelet-driven processes rather than simple hypoxemia. Its absence in rheumatic diseases with pulmonary fibrosis reflects a confluence of protective mechanisms: lack of intrapulmonary shunting, dominance of antifibrotic and antiangiogenic cytokine patterns, pharmacologic suppression of VEGF and PDGF signaling, and fibrotic architectural stabilization of the pulmonary capillary bed. Together, these factors create a biologic environment incompatible with the pathogenesis of clubbing. When clubbing appears in a rheumatic patient, it should prompt immediate investigation for neoplasia, infection, or hepatopulmonary syndrome. This paradox—fibrosis without clubbing—offers unique insight into vascular control in autoimmune disease and invites further study into how these mechanisms might be harnessed to prevent angiogenesis in other chronic disorders.

Table 1. Comparative Mechanisms of Digital Clubbing in Classic Versus Rheumatic Fibrosing Diseases.

Mechanism	Neoplastic, Infectious, or Hepatic Diseases	Rheumatic ILD (RA, SSc, Myositis)
Megakaryocyte passage to systemic circulation	Common due to vascular disruption or shunts [7,9]	Rare; preserved pulmonary filtration
Dominant cytokines	VEGF, PDGF, PGE_2 [5,6]	TGF-β, IL-6, IL-13 [14]
Microvascular pattern	Angiogenic, hypervascular	Obliterative, antiangiogenic [15,18]
Role of therapy	Minimal	Immunosuppressive, anti-VEGF [16–18]
Clinical significance of clubbing	Common finding in malignancy, infection	Exceptional; suggests alternative etiology [13]

Author Contributions

J.F.d.C. and R.A.B.N. have contributed to the conception and design of the study, literature search, data extraction and interpretation, and drafting and critical revision of the manuscript. Y.S. has contributed to the interpretation, drafting and critical revision of the manuscript. All authors have read and agreed to the published version of the manuscript.

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All data generated or analyzed during this study are derived from previously published articles that are cited in the reference list and are available in the public domain.

Conflicts of Interest

Given the role as Editor-in-Chief, Yehuda Shoenfeld had no involvement in the peer review of this paper and had no access to information regarding its peer-review process. Full responsibility for the editorial process of this paper was delegated to another editor of the journal. The authors declare no conflict of interest

Use of AI and AI-Assisted Technologies

AI-assisted softwares (ChatGPT, OpenAI) are used exclusively for language editing and to improve clarity. No content generation, data extraction, or reference creation was performed using AI tools. The authors take full responsibility for the manuscript.

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