

Onco-Rheumatology: From Rags to Riches, A Trans-Disciplinary Evolution

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Abstract

The complexity of modern healthcare necessitates an evolution from managing isolated conditions to understanding the multifactorial interactions between diseases. Onco-rheumatologic patients, who face the simultaneous challenges of cancer and rheumatic diseases, epitomize this complexity. Despite extensive literature documenting the interplay between oncology and rheumatology, there remains a significant gap in integrating care for these patients. This article emphasizes the need for a trans-disciplinary approach, where the integration of knowledge from multiple fields forms new frameworks for patient care. This methodology, while not a definitive answer, provides the most effective way to explore and address the complexities these patients face. Paraneoplastic syndromes and adverse effects of cancer therapies such as immune checkpoint inhibitors further complicate treatment, underscoring the need for coordinated management strategies. Real-world clinical cases, like that of a 48-year-old breast cancer patient with psoriatic arthritis, illustrate the challenges and successes of trans-disciplinary care. Collaboration among oncology, rheumatology, endocrinology, and rehabilitation specialists is critical for long-term patient well-being. The constitution of the Group of Multidimensional Onco-Rheumatology (G-MORE) marks a key step toward fostering dialogue among specialists to advance integrated care. Moving forward, national datasets and best clinical practices must be developed to improve outcomes for this complex patient population and set a new standard in onco-rheumatology care.

Editorial

Managing health today is no longer about treating isolated conditions but about understanding the broader context in which these conditions exist [1]. Healthcare has increasingly confronted complexity in deeper ways, and even the term "complexity" has taken on a more nuanced meaning. The World Health Organization (WHO) advocates for integrated care strategies that weave together diverse elements of health, promoting a systems-based approach. The National Institutes of Health (NIH) emphasizes the intricate interplay of genetic, behavioral, and environmental factors, highlighting the need for interdisciplinary approaches [2]. Meanwhile, the Italian Ministry of Health focuses on the multidimensional nature of patient care, addressing not only physical issues but also the psychological and social needs of patients [3]. As we uncover more about the genetic, environmental, and clinical factors that influence diseases, their management becomes increasingly multifactorial. With each new insight, the scope of what we must consider grows. In oncology and disease-modifying therapies, treatments now extend beyond controlling the disease: they alter the patient's biology, often introducing new challenges in care. These therapies impact not only the disease but also the patients themselves, adding layers of complexity to their overall health. What once seemed straightforward in patient-care now involves navigating a web of interrelated elements [4].

Onco-rheumatologic patients, those facing the simultaneous challenges of cancer and rheumatic diseases, are the clearest example of complexity in modern healthcare [5-7]. The questions surrounding their care, epidemiological, clinical, pathological, and therapeutic, remain largely unanswered. How can we best navigate the overlapping conditions they face?

What are the long-term impacts of treating cancer in the presence of autoimmune disease, or vice versa? While the European League Against Rheumatism (EULAR) has made efforts to address aspects of these conditions, the solutions are not yet clear [8]. What is clear, however, is that the trans-disciplinary approach provides the most effective methodology to explore these questions. It is not the definitive answer, but it offers the framework to uncover the insights and strategies needed to manage the complex realities these patients face [9-12].

The interplay between oncology and rheumatology has been well-documented for decades, yet there remains a significant gap in integrating care for these patients [4,13-19]. The relationship between cancer and rheumatic diseases has been acknowledged since 1944, with over 9,000 articles available on PubMed documenting various aspects of this connection. Despite this extensive literature, an integrated onco-rheumatologic approach has been discussed in only one paper, underscoring a significant gap [20]. Paraneoplastic Syndromes (PNS) have historically demonstrated the complex interplay between cancer and rheumatologic symptoms. PNS affects approximately 10-15% of cancer patients, significantly impacting their prognosis. Rheumatologic PNS (RhPNS) includes conditions such as tumor-induced osteomalacia, cancer-associated myositis, and paraneoplastic arthritides, showcasing the multifaceted challenges faced by these patients [21-23]. Advancements in cancer therapies further underscore the intersection of these fields. Immune Checkpoint Inhibitors (ICIs) and hormone manipulation therapies have shown significant overlap with rheumatologic conditions. ICIs, used in treating non-small cell lung cancer, have demonstrated that 70% of patients experience

Rheumatic Adverse Events (RhAEs), reflecting immune system activation [24]. These adverse events, while challenging, may also indicate a robust immune response against cancer cells. Similarly, hormone manipulation therapies, such as aromatase inhibitors in breast cancer and androgen deprivation therapy in prostate cancer, lead to rheumatologic complications like joint pain, osteoporosis, and autoimmune disorders [25]. These examples highlight the necessity for integrated management strategies. Epidemiological data reveal a bidirectional relationship between cancer and rheumatic diseases [23]. Cancer patients often develop rheumatologic issues, and there is a higher prevalence of cancers among patients with rheumatic diseases. Patients with rheumatoid arthritis, lupus erythematosus, and Sjögren's syndrome, for instance, have a significantly increased risk of various cancers, including lymphoma and lung cancer. This increased risk is partly due to the therapies used to manage their rheumatic conditions [14]. There has been concern regarding the potential cancer risks associated with immunosuppressive therapies for rheumatic diseases [19]. However, strong evidence has never conclusively emerged, and confusion still persists on the topic today. Methotrexate (MTX), the most used traditional DMARD, is no longer deemed to increase the overall cancer risk in rheumatoid arthritis patients, contrary to initial reports [26]. Moreover, there's no clear evidence linking the newer "biologic" DMARDs with an increased risk of cancer recurrence or new cancer development. In fact, Rituximab is often the drug of choice for patients with a history of lymphoproliferative disorders, as recommended by the American College of Rheumatology [27]. However, recent studies have raised concerns, particularly one trial indicating an increased cancer

risk associated with Tofacitinib, a Janus Kinase (JAK) inhibitor. Consequently, the use of JAK inhibitors is generally avoided in cases where there is an additional risk factor for cancer, although ongoing research and subsequent clinical trials demonstrate a risk comparable to placebo and methotrexate, underlining how the risk is more linked to the disease activity itself [28]. Thus, this area remains a subject of debate and requires further clarification. Biological evidence points to shared pathways between cancer and rheumatic diseases. Both conditions involve immune imbalances and inflammatory processes, with mechanisms such as the presentation of new antigens by tumor cells and activation of cytokines and chemokines driving inflammation [29,30]. These commonalities highlight the potential for integrated therapeutic approaches.

While theoretical and epidemiological evidence highlights the complexity of onco-rheumatology, it is through real-world clinical cases that we truly see how problem-solving in such complex scenarios demands a trans-disciplinary approach: a 48-year-old non-smoking female patient with a history of psoriatic arthritis and hypothyroidism, was diagnosed with right breast cancer in 2017. Her complex medical history required the coordinated efforts of multiple specialists to ensure optimal care. Initially managed for psoriatic arthritis with Salazopyrin, her treatment plan needed to be carefully adjusted when she was diagnosed with breast cancer. The oncology team, in collaboration with her rheumatologist, decided to continue her arthritis therapy while she underwent a total mastectomy, lymphadenectomy, and subsequent chemotherapy. During chemotherapy, the patient's arthritis therapy was gradually tapered and eventually discontinued due to signs of remission. Following

chemotherapy, the patient was transitioned to tamoxifen, necessitating the introduction of denosumab and vitamin D to manage potential bone density issues. Throughout her cancer treatment, she also received support from a nutritionist and underwent rehabilitation for lymphedema, highlighting the role of lifestyle modifications and physical therapy in her overall care. As the patient reached the five-year mark post-cancer treatment, she discontinued tamoxifen and continued with Decapeptyl and denosumab. However, in June 2024, the oncology team sought input from her rheumatologist regarding the continuation of denosumab therapy, given her recent cessation of Decapeptyl and the results of a bone density scan. This case underscores the critical role of both multidisciplinary and trans-disciplinary approaches in managing patients with complex medical histories. The successful coordination between oncology, rheumatology, endocrinology, nutrition, and rehabilitation specialists allowed for a tailored treatment plan that addressed the patient's diverse needs. Such collaboration ensured that each aspect of her health was considered, leading to better overall outcomes and quality of life.

Managing onco-rheumatologic patients remains a significant challenge due to the complexity of their conditions, which demands a comprehensive trans-disciplinary approach. This concept of trans-disciplinarity, where knowledge from various disciplines is integrated to create new frameworks, is crucial for addressing their multifaceted needs [10]. The goal is not just short-term results but ensuring long-term patient well-being as their conditions evolve. How can we, as healthcare professionals, ensure these patients receive the comprehensive care they need? Ongoing communication and synergy

between specialists are key. This coordinated effort has led to the establishment of the Group of Multidimensional Onco-Rheumatology (G-MORE), which serves as a facilitator of dialogue, bringing together specialists to navigate the intricate web of onco-rheumatologic care. Through this collaborative approach, we aim to support the advancement of a more integrated, patient-centered care.

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