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Multiple Myeloma and Visceral Leishmaniasis: When and Why Differential Diagnosis May be Challenging

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About the Study

Multiple Myeloma (MM) is commonly associated with immunoparesis, that consists in suppression of uninvolved polyclonal immunoglobulins, and immune cell dysregulation which may impair the ability to contrast pathogens. In addition, anti-MM therapy may cause neutropenia, lymphopenia and hypogammaglobulinemia, causing an increased susceptibility to opportunistic infections in these patients. Moreover, independently by the biochemical response, anti-myeloma therapy is often administered until progression or intolerance (e.g. lenalidomide maintenance) leading the immune system to an incomplete fully recover.

Visceral Leishmaniasis (VL) is a vector-borne, mainly endemic, parasitic infection existing both in the zoonotic and the anthroponotic form. The zoonotic form, caused by *Leishmania infantum*, is the most frequent entity in Europe and it is transmitted through the bite of female hematophagous sand flies from the genus Phlebotomus. VL, which is potentially fatal without proper treatment, is characterized by intermittent fever, splenomegaly and weight loss combined to laboratory alterations such as hypergammaglobulinemia, elevated inflammatory markers and (pan) cytopenia. As we have previously reported, some common characteristics between VM and VL can lead to diagnostic-therapeutic errors. Let's try to analyse the key points of our case report in detail [1].

Polyclonal hypergammaglobulinemia is a common feature of VL; anyway, the detection of monoclonal paraproteins is exceptional but possible in this setting of patients. Indeed, several case reports beyond ours depicted VL as an etiology of both monoclonal gammopathy or reactive plasmacytosis in bone marrow firstly misdiagnosed with MM.

It is important to underline that monoclonal IgG paraprotein may have an extremely long duration also after the infection resolution. These manifestations have been proposed to be a result of chronic antigenic stimulation that occurs in these patients. Since host defense against *Leishmania* is mediated by T cells and T-cell-derived cytokines such as interferon gamma (IFN-γ) directed against infected macrophages, alterations of these mechanisms may promote the development of VL chronicity, as occurred in our patient [2]. Interestingly, paraproteins and hypergammaglobulinemia appeared when lenalidomide was suspended, probably due to reactivation of the immune system.

Hippocratic medicine considered error as an intrinsic element of diagnostics. Physicians who are influenced by long or frequent experiences with a certain kind of disease may be more likely led to a misleadin g diagnosis: The so called “availability bias”. Indeed, all signs and symptoms (anaemia, fatigue and loss of appetite) were immediately associated to lenalidomide intolerance and, similarly, the increase of the paraprotein was associated to probable MM relapse. Conversely, splenomegaly wasn’t sufficiently investigated by physicians, despite it was the key element to catch the correct diagnosis. During medical school studies, a lot of physicians are taught the old saying “when you hear hoof beats, think horses, not zebras”, which means to consider the most likely possibility first when thinking of a diagnosis. In a posteriori justification, the coexistent of splenomegaly , constitutional symptoms, cytopenia and the presence of monoclonal gammopathy, even with the absence of fever for the reasons above mentioned, should have suggested the probability of Leishmania infection, which is the “zebra” in endemic region.

In general, when in the blood tests paraprotein is present, the majority of physician (haematologist or non-haematologist) believe firstly to diagnosis Monoclonal Gammopathy of Undetermined Significance (MGUS), which is considered an obligate precursor to several lymphoplasmacytic malignancies. Anyway, it must be considered the paraprotein is present in other non-hematologic conditions such as autoimmune disorders (Rheumatoid arthritis, Scleroderma, Hashimoto's thyroiditis), cutaneous disease (Pyoderma gangrenosum, Necrobiotic xanthogranulomatosis), liver disease (Hepatitis, cirrhosis) chronic infections(Tuberculosis, endocarditis) or

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in or in patients who underwent organ transplantation [3]. For this reason, diagnostic work-up and long-term follow-up is generally recommended. Similarly, the absence of fever in our patient might be due to the above-mentioned dysregulation of the immune system, as reported in HIV-positive or post-transplant condition. Thus, the second key point to keep in mind is that whether fever is usually the alarm bell to check or to suspect the presence of infection, not all infections present with fever. Indeed, in immunocompromised patients, the immune system may be anergic. Whatever the discovery of Acquired Immune Deficiency Syndrome (AIDS) in the 80s led to the knowledge of opportunistic infections, they should still be considered in patients who were treated with immunosuppressive drugs.

Moreover, we could assert that any clinical splenomegaly should be considered always pathological and must be deeply investigate. In patients with understanding splenomegaly and cytopenia, anti-Leishmania antibodies combined to DNA *Leishmania* research should be tested in endemic area. Finally, in blood diseases, a thorough bone marrow examination (aspiration and biopsy) remains the key diagnostic tool despite the advent of modern techniques. A condition in which splenomegaly may be associated to paraprotein is POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes), a rare paraneoplastic syndrome caused by a clone of aberrant plasma cells; anyhow, polyneuropathy is a mandatory criterion and its absence exclude POEMS syndrome in differential diagnosis.

Currently, the risk to develop infections in MM and other hematologic malignancies, is increasing in the era of bispecific antibodies and Chimeric Antigen Receptor T-cell (CAR-T) therapy which may develop deep hypogammaglobulinemia or longer cytopenia [4]. Whether infections in MM are mainly caused by viruses and bacteria, fungal and also parasitic infections such as Strongyloidiasis, Trypanosomiasis, and Toxoplasmosis have rarely been reported and their incidence may be increase in the future. Anyway, neither routine work-up or prophylaxis are recommended for parasitic infection, but they should be considered in the case of the exposed patient or endemic region.

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