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Debut of multiple myeloma with invasive pneumococcal disease in an atypical location

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Abstract

Multiple Myeloma (MM) is associated with infections, especially by encapsulated bacteria. A male patient with septic arthritis of knee and carpus by *Streptococcus pneumoniae* developed two pneumococcal pneumonias. Unconjugated pneumococcal vaccine was administered. Repeated Invasive Pneumococcal Infections (IPI) and biarticular location raised the possibility of acquired immunodeficiency, with MM finally diagnosed. After five cycles of chemotherapy, the patient developed spondylodiscitis and leptomeningitis secondary to an IPI. Conjugate vaccine was administered in August 2013. He subsequently received autologous hematopoietic cell transplantation and was revaccinated post-transplant with pneumococcal conjugate and other recommended vaccines, not suffering from more serious infections.

When faced with a patient without risk factors, with repeated infections by encapsulated bacteria with articular or polyarticular location, MM should be considered as a differential diagnosis. After the diagnosis of MM, recommended conjugate vaccines must be given as soon as possible, so that premature mortality due to infections may be prevented.

Keywords

Multiple myeloma; Immunization; Vaccines; Infection.

Introduction

Multiple Myeloma (MM) is associated with an increased incidence of infection in the early stages after diagnosis that is responsible for high mortality during this period [1]. Association of infections years before the diagnosis of MM has also been described. However, in very few cases has infection been described as a presenting feature of MM [2]. A patient is presented in which the characteristics of infection led to suspecting the possibility of this oncohematologic disease, emphasizing the importance of bearing it in

mind in the differential diagnoses at the onset of an infection with certain characteristics.

Clinical Observation

Male, born in April 1946. No known allergies. Ex-smoker of 20 packets/year for nine years before the onset of the clinical manifestation, traumatic fracture of right carpal (20 years ago), carpal tunnel syndrome, headache in clusters, bilateral inguinal herniorrhaphy, appendectomy, tonsillectomy, resolved hepatitis B infection, and disc herniation treated with rhizotomy. He was hospitalized by the rheumatology service because of septic arthritis of the left knee and right carpus, requiring surgical cleaning of both joints and showing positive cultures for *Streptococcus pneumoniae*. One year later, the patient was admitted to the pneumology service through the emergency department for community-acquired pneumonia, detecting positive for pneumococcal antigen in urine (++). The patient developed a systemic inflammatory response syndrome during admission with severe sepsis, from which he recovered after 15 days of hospital stay. The existence of pneumococcal invasive infection repetition, its initial multi-joint location, along with the presence of discrete anemia did lead to suspecting possible cellular or humoral acquired immunodeficiency, so the hematology service was consulted. In the analytical study, hypergammaglobulinemia IgG type was observed, along with lowering of IgA and IgM levels, deficit of complement factors, and hypoalbuminemia. Therefore, a request was made for protein electrophoresis, 24-hour study of urine, and immunofixation in blood and urine, confirming the presence of a monoclonal IgG component. Bone marrow aspirate was performed on the day of discharge, and the patient was referred preferentially to the hematology consultation to complete the extension study on suspicion of MM and to inform him of the study results. Unconjugated pneumococcal polysaccharide vaccine was administered to the patient. Twenty-six days after discharge, and less than two weeks after administration of the vaccine, the patient developed community-acquired pneumonia, requiring hospital admission through the emergency department. Pneumococcal antigen (+++) was detected in urine again and S*. pneumoniae* was isolated in a series of three blood cultures. During admission, the diagnosis of MM IgG lambda stage II-A ISP II was confirmed. The patient suffered neurological *cauda equina* syndrome with polyneuropathy because of myeloma complication during admission with perineal anesthesia and neurogenic bladder, so combination chemotherapy was started: five cycles of dexamethasone-cyclophosphamide-bortezomib with partial response (50%) along with oral entecavir prophylaxis. In June 2013, he was re-admitted due to L4-L5 spondylodiscitis and cauda equina leptomeningitis secondary to invasive pneumococcal infection. Initial treatment was changed to bortezomib + lenalidomide + dexamethasone for four cycles with subsequent mobilization, harvesting, and cryopreservation of hematopoietic progenitors. Patient received pneumococcal conjugate vaccine six months after pneumococcal pneumonia episode considering the possibility of vaccine failure of the plain polysaccharide 23-valent vaccine that had been administered. One year after from pneumonia episode, he underwent an autologous transplant of hematopoietic progenitors, and received two cycles of consolidation with the same pattern of chemotherapy as used before. Maintenance treatment was started but was suspended six months later because of the development of neuropathy. Three months after transplantation, the patient was referred to the preventive medicine unit for vaccination and received three doses of pneumococcal 13-valent conjugate vaccine. Other indicated vaccines were also administered after transplantation: Influenza, *Haemophilus influenzae* type b, tetanus-diphtheria, inactivated polio, and

hepatitis B. Patient was given an appointment to ask for his consent and check for the development of relevant infections, not having suffered any more serious vaccinable infections since administration of the conjugate vaccines.

Discussion

The association between MM and infection is clearly established; notably, the risk of bacterial and viral infections is 7 and 10 times higher, respectively [3]. Infection causes 45% of all deaths in these patients and is related to deficits in cellular and humoral immunity, reduced mobility, and performance level that are associated with the disease and its treatment, especially with glucocorticoids [4-6]. Despite this, the temporal relationship between MM and infection is still an issue under debate. Thus, increased risk of development of infections has been associated to different stages in the course of the disease: years prior to diagnosis of MM, noting association of bronchitis, pharyngitis, pneumonia, sinusitis, cold, herpes, cellulitis, and cystitis in the period between 31-48 months preceding the diagnosis of MM or Myelodysplastic syndrome [7]; or early after diagnosis, with some studies pointing out that up to 10% of patients die from infections within 60 days following diagnosis [4], rising to 22% during the first year [3]. However, in only a few cases have invasive infections been described as a characteristic of MM presentation [2]. In these patients, infection is caused by encapsulated organisms and most likely occurs in joints as septic arthritis. Thus, invasive *S. pneumoniae* infections have been reported as the first manifestation of MM in the form of septic arthritis or bacteremia [8-11]; or *Haemophilus influenzae* with initial joint location [12-14] but also in the form of pneumonia [12], and sepsis [13,14]; and less frequently by *Neisseria meningitidis* [15].

Defects in opsonophagocytic function and humoral immunity appear to be related to excess specific risk of infections caused by capsulated bacteria [2,8-15]. Alterations in bone resorption inherent to the disease, which are sometimes detected at the time of diagnosis, could justify the location of these infections in joints with greater frequency than expected in the general population [8-10,12-14]. Thus, when faced with a previously healthy patient with repeated bacterial infections and without other risk factors, MM should be considered among the differential diagnoses [16], especially when these infections are caused by capsulated bacteria and have a joint location or affect more than one joint.

In the case presented here, no quantification of specific antibodies against serotypes of *S. pneumoniae*, or determination of the serotype of the isolated bacteria were available, so the occurrence of vaccine failure cannot be confirmed or ruled out. Immunogenicity of unconjugated pneumococcal vaccines in MM patients has proved to be poor, generating protective titles in approximately 40% of vaccinated patients. However, conjugate vaccines such as *H. influenzae* type b vaccine have demonstrated good immunogenicity, coming to generate protective antibodies in 75% [17,18]. So early vaccination with conjugate vaccines minimizes the vaccine failures that are characteristic of plain polysaccharide vaccines in these patients. After diagnosis of MM, administration of the recommended vaccines should be initiated as soon as possible, including conjugate vaccines against *S. pneumoniae*, *H. influenzae* type b, and *N. meningitidis* [6,16]; this practice has led us to avoid premature mortality by infectious cause in these patients. In addition, preventing these infections could be an indirect benefit in these patients by eliminating some of the possible

triggers that are suspected may be related to the transformation of premalignant cells to malignancy.

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