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An Unusual Presentation of Multiple Myeloma with High Grade Fever and Loss of Consciousness

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Authors' contributions

This work was carried out in collaboration between all authors. Authors HRN and FS wrote the draft of the manuscript. Authors RK, SS and MM managed the literature searches. Authors HRN and FS designed the figure, managed literature searches and contributed to the correction of the draft. Authors RK, SS and MM provided the case. Authors HRN and FS supervised the work. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Patients with multiple myeloma (MM) are susceptible to bacterial infections, particularly those caused by encapsulated pyogenic bacteria such as *Streptococcus pneumoniae*. Significant morbidity and mortality attributable to these infections has been reported in patients with MM. Insufficient synthesis of polyclonal immunoglobulins reflected in marked hypogammaglobulinemia is an important underlying mechanism responsible for the compromised immune system in patients with MM. Despite the fact that patients with MM are prone to develop sepsis caused by encapsulated bacteria, an acute bacterial infection is rarely reported as the first manifestation of underlying MM. Here, we report a rare presentation of MM with hyperacute bacterial meningitis.

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1. CASE REPORT

The patient was a 54-year-old white male teacher in his good health up to the day of presentation. The symptoms started after he came back home from school complaining of sudden onset explosive headache with fever, chills, nausea and vomiting. Few hours later, he became disoriented and lost his consciousness. At the time of hospital admission, he was agitated and disoriented as well as deeply confused. His body temperature was 38ºC, blood pressure was 170/100 mmHg, pulse 100 per min, respirations 24 per min, and the oxygen saturation was 93% on room air. He had mild conjunctival pallor, his neck was stiff, Kernig sign was positive, and papilledema was not found. Neurological examination was otherwise unremarkable. The remainder of the examination was normal. During the next several hours, he was in deep coma. Due to altered sensorium in the setting of presumed acute bacterial meningitis, the patient was intubated and ceftriaxone, vancomycin, and dexamethasone were started. Admission lab exams were notable for a white blood cell count of 9,100 /mL with 75% neutrophils; hemoglobin 7.9 g/dL, hematocrit 23.2%; and platelet count 161,000 /mL. His serum values were as follows: sodium, 133 mmol/L; BUN, 20 mmol/L; creatinine, 1.4 mmol/L; glucose, 349 mg/dL; and calcium, 8.1 mg/dL. Alanine aminotransferase was 41 U/L, aspartate aminotransferase 22 U/L, and alkaline phosphatase 102 U/L.

A chest radiograph demonstrated no cardiomegaly or significant pulmonary infiltrates. A brain computed tomography had no abnormal finding. His cerebrospinal fluid (CSF) analysis showed 200 cells/µl, with 85% neutrophils, glucose 14 mg/dL, and protein 106 mg/dL. Gram's staining of the CSF revealed trivial inflammatory response despite the large number of lancet-shaped gram-positive diplococci (Fig. 1). On the subsequent day, his CSF and blood cultures isolated penicillin susceptible *Streptococcus pneumoniae*. Ceftriaxone and vancomycin stopped and high dose intravenous penicillin started.

It took more than 10 days after starting antibiotics that patient gradually regained his consciousness and extubated. He completed a 14-day course of antibiotics. During this period, he also developed extensive herpes labialis for which he received acyclovir.

Regarding several clues in the scenario including severe life-threatening meningitis with few polymorphonuclears in the presence of abundant organisms on CSF smear, anemia, and persistent high level inflammatory biomarkers, the possibility of an underlying disorder with associated immune compromise was considered

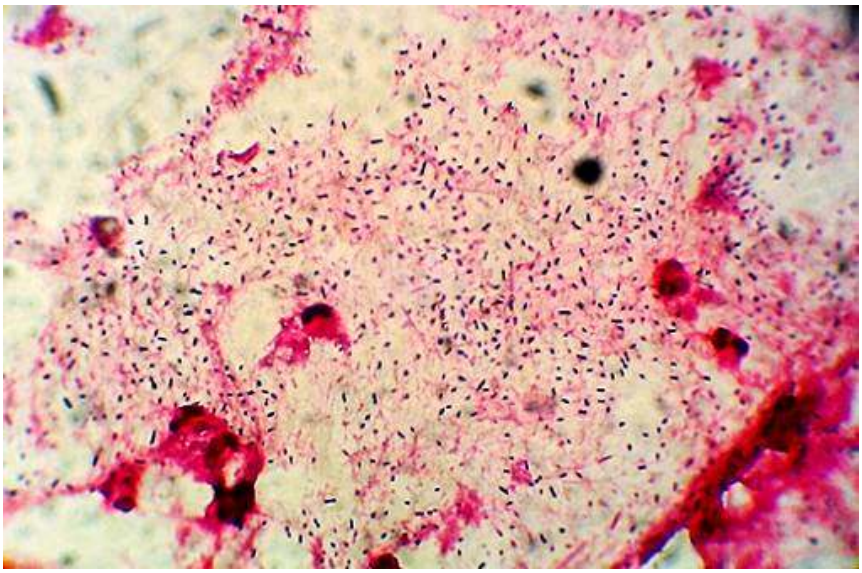

Fig. 1. Gram's staining of the CSF revealed trivial inflammatory response despite the large number of lancet-shaped gram-positive diplococcic

and patient was evaluated accordingly. MRI of lumbar spine showed pathologic fracture at L4. Serum protein electrophoresis revealed monoclonal IgG lambda, whereas IgA and IgM levels were diminished. (IgG:963 mg/dL, IgM:25 mg/dL, and IgA:494 mg/dL). Bone marrow biopsy performed and revealed diffuse infiltrate of plasma cells that comprised 45% of the cellular elements. At that point, dexamethasone and thalidomide were started by hematologist. Treatment led to remission of MM and consecutive courses of treatment were planned. The patient received pneumococcal polysaccharide vaccine and no further bacterial infections occurred during more than 12 months follow up.

2. DISCUSSION

This case represents a rare presentation of MM with hyper-acute pneumococcal meningitis with several poor prognostic features. Morbidity and mortality in MM is often attributed to life-threatening infections. Most of the infections are of bacterial origin, and the most serious are septicemia, meningitis, and pneumonia [1-3].

Myeloma-related innate immunodeficiency involves various arms of the immune system and includes B cell dysfunction (manifested by a slow rise in immunoglobulin M (IgM) titers, and a reduced capacity to synthesize other immunoglobulin classes needed for secondary immune response), numerical and functional deficits in complement activity, numerical and functional abnormalities of dendritic cell and T cells (inversion of CD4:CD8 ratio, abnormal Th1/Th2 $CD4^+$ ratio, and severe disruption of global T cell diversity), and dysfunction of natural killer cells. These put patients with MM at high risk of infection especially by encapsulated bacteria such as *S. pneumoniae* or *Haemophilus influenzae* [3- 5].

The propensity to infection is increased in the first months after the initial diagnosis and in patients with renal dysfunction. Gram-positive infections, mainly pneumonia from *S. pneumoniae*, occur more frequently in patients with untreated disease while Gram-negative infections, mainly of the urinary tract, are more common after chemotherapy [1]. Hargreaves et al. [6] observed that over three-quarters of all serious infections happened 3 months after the initial diagnosis. In the cohort by Savage et al. [7] most of the infections with *S. pneumoniae* and *H. influenza* occurred in the first 8 months of disease, and almost all patients were receiving chemotherapy. However, an acute bacterial infection is rarely reported as the first manifestation of underlying MM [1]. Previously, Costa et al. [8] reported two cases of pneumococcemia as the presenting feature of MM of whom one had bacteremic pneumococcal pneumonia and the other presented with bacteremic pneumococcal meningitis. They added the common features of their two patients to the few patients described in the literature with pneumococcemia as the first sign of MM and described several common findings that should lead to a suspicion of MM in an otherwise asymptomatic patient, including *S. pneumoniae* bacteremia, leukopenia, mild anemia, history of prior bacterial infections, and indirect evidence of a paraproteinemia, such as increased total protein levels with low albumin [8]. Kalambokis et al. [1] analyzed data from 17 such cases of MM presenting with acute bacterial infection reported between 1978 and 2008. Musculoskeletal infections predominated in these early cases followed by pneumonia. In particular, septic arthritis, mainly of the knee, was the most common infectious complication. *S. pneumoniae* was isolated in two-thirds of infections and bacteremia was common. We also reviewed 30 patients (1978-2015) in whom infection has resulted in unmasking of an underlying MM (Table 1).

S. pneumoniae is an important and well-known cause of bacteremia in both immunocompetent and immunosuppressed patients [33]. The study of Gregersen et al. in the County of North Jutland, Denmark showed that patients who survive an episode of community-acquired pneumococcal bacteremia or meningitis are at increased risk of being diagnosed with MM, but the absolute risk is low. They identified 328 episodes of community-acquired pneumococcal bacteremia and 77 episodes of pneumococcal meningitis in 227,000 persons over 40 years of age. The incidence rate of a subsequent diagnosis of MM was 7 cases per 1,218 patient-years during the follow-up period in the bacteremia cohort, compared with 0.13 cases expected. During 444 patient-years of follow-up in the meningitis cohort, 4 cases of MM were diagnosed compared with 0.05 cases expected [2].

Previously, it has been suggested that recurrence of bacteremic infections caused by *S. pneumoniae* is a warning sign of immunodeficiency [34]. Here, a question comes

in mind: is it also necessary to evaluate all adult patients with first episode of invasive pneumococcal disease for underlying diseases? Guerrero et al. [35] conducted a study to evaluate the clinical and bacteriologic characteristics of bacteremic pneumococcal infections in immunocompromised patients without AIDS. A comparison of clinical manifestations of pneumococcemia between immunocompromised patients and non-immunocompromised patients did not show differences in the presence of fever, obtundation, type of lung involvement, frequency of primary bacteremia, or meningitis.

Patel and Nikcevich [4] reported a case of pneumococcal meningitis as initial presentation of MM. The reason that they suspected an underlying immunodeficiency was the presence of stained smear of CSF disclosed multiple extracellular-Gram-positive diplococci reflecting defective complement activation. Our patient

Table 1. Some characteristics of cases presented as the first feature of MM reported in the literature

Authors	Age	Sex	Clinical syndrome	Pathogen
Posner et al. [9]	59	M	Meningitis, bacteremia	*S. pneumoniae*
Martiz and Joubert [10]	NA	NA	Pneumonia	*H. influenza*
Barasch et al. [11]	70	F	Pneumonia, becteremia	*S. pneumoniae*
	50	F	Becteremia	*S. pneumoniae*
	70	F	Pneumonia, bacteremia	*S. pneumoniae*
Miller et al. [12]	64	M	Septic arthritis	*N. meningitidis*
Sarubbi et al. [13]	67	M	pyomyositis	*S. marcescens*
Cuesta et al. [14]	47	F	Septic arthritis	*S. pneumoniae*
Berthaud et al. [15]	43	F	Septic arthritis, bacteremia	*H. influenzae*
Fukuzawa et al. [16]	63	M	Endocarditis complicated by congestive heart failure	*S. salivarius*
Bhatnagar et al. [17]	NA	F	Septic arthritis, pneumonia	*H. influenzae*
Durupt et al. [18]	68	M	Cellulitis	*S. pneumoniae*
Patel et al. [4]	NA	NA	Meningitis	*S. pneumoniae*
Costa et al. [8]	68	F	Pneumonia, bacteremia	*S. pneumoniae*
	57	M	Meningitis, bacteremia	*S. pneumoniae*
Austein et al. [19]	60	F	Bacteremia complicated by severe sepsis	*Streptococcal species*
Renou et al. [20]	62	M	Septic arthritis	*S. pneumoniae*
Aue and Austein [21]	60	F	Bacteremia	*S. pneumoniae*
Bigaillon et al. [2]	88	M	Meningitis, pneumonia, bacteremia	*S. pneumoniae*
Sumrall et al. [23]	75	M	Polyarticular Septic arthritis, bacteremia	*S. pneumoniae*
Kalambokis et al. [24]	67	F	Pyomyositis	*CA-MRSA*
Ottaviani et al. [25]	55	NA	Polyarticular septic arthritis	*Moraxella canis*
Yu et al. [26]	NA	F	Infectious spondylitis	*E. coli*
Riachy [27]	43	M	Polyarticular septic arthritis complicated by septic shock	*S. pneumoniae*
Chan et al. [28]	64	M	Native aortic valve endocarditis complicated by mycotic abdominal aortic aneurysm, paraspinal and iliopsoas abscesses and pneumonia	*S. pneumoniae*
Prinsen et al. [29]	NA	M	Infectious spondylitis	*M. tuberculosis*
Shahani et al. [30]	67	M	Bacteremia	*S. pneumoniae*
Suwantarat et al. [31]	65	M	Pneumonia, bacteremia	*Herbaspirillum seropedicae*
Daniel et al. [32]	54	M	Bacteremia	non-O1/non-O139 *Vibrio cholerae*
The present case (2015)	54	M	Meningitis, bacteremia	*S. pneumoniae*

showed several predictors of poor prognosis and lack of complete immune response. It has been previously noted that very low CSF WBCs (0 to 20 /mm3) despite high CSF bacterial concentrations tend to have a poor prognosis [36]. Low CSF white cell counts despite high CSF bacterial concentrations in patient with bacterial meningitis might also be a warning sign of underlying immunocompromise state.

3. CONCLUSION

It can be proposed that at least some patients with unusual and invasive bacterial infections presenting with features indicative of compromised immune response such as the presence of trivial inflammatory response despite the large number of organisms at the site of infection should be the subject of further evaluation for underlying disease. However, despite the fact that patients with MM are prone to develop sepsis caused by encapsulated bacteria, an acute bacterial infection is rarely reported as the first manifestation of underlying MM. Hence, this cannot be a recommendation, but rather a subject of future study to evaluate the predictors of underlying conditions in patients with unusual and severe bacterial infections.

CONSENT

All authors declare that 'written informed consent was obtained from the patient for publication of this case report and accompanying image.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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