Nocardiosis Associated with Novel Agents at Relapsed Multiple Myeloma: Case Series

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Authors’ contributions

This work was carried out in collaboration among all authors. Author AT designed the study, wrote the protocol and wrote the first draft of the manuscript. Authors ZB, EC, MT, BGK, CK and IY managed the analyses of the study. Author IY managed the literature searches. All authors read and approved the final manuscript.

ABSTRACT

Nocardiosis is a gram positive bacterial infection caused by aerobicactinomycetes. Its nonspecific presentation and radiographic findings usually make it undiagnosed with highly fatal outcomes. The patients with intracelluler defects are prone to nocardiosis. Multiplemyelom(MM) itself is a mainly humoral deficiency disorder because of defective antibodies but recent drugs such as proteasome inhibitors and immuno modulatory drugs also cause cellular deficiency. Here we presented two definite and oneprobable pulmonary nocardiosis patients who have a diagnosis of MM, autologou hematopoetic stem cell transplant history in their past and anti myeloma therapy presently.

Keywords: Nocardiosis; multiple myeloma; gram-positive bacterial infection; actinomycetes.

Case Study

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1. INTRODUCTION

Nocardiosis is an uncommon gram-positive bacterial infection caused by aerobic actinomycetes. Nocardia spp can cause localized or systemic suppurative infections, mostly in immunosuppressed individuals [1]. There are limited data about the incidence of nocardiosis around the world including Turkey, but it is reported between 500 and 1000 new cases each year in the USA, while in France and Italy it ranges between 150 and 200 and 90 and 130 annual cases, respectively [2]. The microorganism can enter to the body via the soil, house dust, beach sand, swimming pools or direct inoculation of the skin [3]. Pulmonary infection is the most common presentation, but dissemination to any site of the body can be seen, especially to the central nervous system [4]. Patients with intracranial defects like diabetes and acquired immune deficiency syndrome (AIDS) are prone to invasive nocardiosis [5]. Multiple Myeloma (MM) itself is an immunosuppressive disorder because of the defect mainly on the humoral immunity and antibody production. Currently, immunomodulatory drugs and proteasome inhibitors are being used extensively, but they might increase the infection risk by several mechanisms [6]. Here, we present three relapsed myeloma cases which developed an unusual infection during their treatment: Nocardia pneumonia.

2. CASE-1

Sixty six year old man, who has a history of autologous stem cell transplantation (SCT) after the induction with vincristine-adriamycin-dexamethasone (VAD) regimen 4 years ago and lenalidomide- dexamethasone usage because of IgG kappa type myeloma, has been prescribed bortezomibe for the relapse of the disease. He was immunocompromised not only because of the myeloma, and also because of the diabetes and renal failure without dialysis. He was admitted to the hospital because of the productive cough. His lymphocyte count was 1290/mm3 and flow-cytometric analysis showed CD5: 68% and CD20: 2%. High resolution computed tomography (HRCT) showed 39x39x45 mm diameter sized, mass like, well bordered lesion which contains air bronchograms at superior lobe posterior segment of the right lung. Bronchoscopic lavage examination showed branched bacilli via modified acid-fast and Gram stain. This typical morphological appearance was defined as *Nocardia spp.* Imipenem/cilastatin and trimethoprim/sulfamethoxazole (TMP/SMX) treatment started and control CT was performed after ten days and it showed regression of the infiltration. He was discharged with oral TMP/SMX therapy as planned to use for minimum 6 months together with the use of anti-myeloma therapy. There was no relapse of nocardia after 6 months and antibacterial therapy was stopped thereafter. The patient died 8 months later because of kidney failure unrelated to nocardia.

3. CASE-2

71 year old woman, who has a history of two autologous SCT 12 and 5 years ago because of IgG kappa type myeloma; admitted to the hospital with productive cough complaint during pomalidomide treatment. Her lymphocyte count was 2300/mm3 and flow-cytometric analysis showed CD5: %88 and CD 20: %1. HRCT showed a 7x6x6 cm diameter sized mass like infiltration which also contains cavity at superior apical location of the right lung. The patient has been started piperacillin-tazobactam therapy. Branched Gram positive bacilli (*Nocardia sp.*) was detected from bronscopic lavage specimen analysis, so the antibiotic therapy changed to imipenem-cilastatin. She responded well to therapy and was discharged with oral TMP/SMX therapy as planned to use for minimum 6 months together with the use of anti-myeloma therapy and after 6 months without nocardia recurrence, antibacterial therapy was stopped. The patient died of hypercalcemia and progressive myeloma 2 years later.

4. CASE-3

72 year old man, who has a diagnosis of IgG kappa type myeloma and a history of autologous SCT 4 years ago following bortezomibethalidomide-dexamethasone treatment, relapsed 5 months ago. He has been admitted to the hospital with non-productive cough complaint under the treatment of lenalidomide and dexamethasone. His lymphocyte count was 520/mm3. Flow-cytometric analysis couldn’t be performed. HRCT showed a 4 cm diameter sized collapse-consolidation field which contains cavity fully filled with liquid at superior lobe posterior and inferior lobe superior segment of the right lung. Sputum microscopy showed acid resistant branched bacilli thought to be consistent with nocardia. Tests were negative for tuberculosis. The diagnosis was accepted as probable nocardia infection.
and imipenem/cilastatin and TMP/SMX treatment have begun and 12 days later, a control HRCT was performed and showed regression. He was discharged with oral TMP/SMX therapy as planned to use for 6 months but after 3 months he died because of progressive myeloma unrelated to nocardia infection.

5. DISCUSSION

Patients with MM are susceptible of infections and the risk is higher for the first 3-4 months of induction therapy and in the setting of relapsed disease [7]. Pneumonias and urinary tract infections account for the majority infections with *streptococcus pneumoniae*, *haemophilus influenzae*, and *escherichia coli* being the most common organisms. Except the immunosuppressive treatments; active disease, steroid and bisphosphonate usage, renal failure, iron overload and in the setting of allogenic stem cell transplantation GVHD are the other risk factors that facilitate infection [6]. Lenalidomide, a novel immunomodulatory drug, when combined with dexamethasone, is proven to make the patient susceptible for bacterial infections in the relapsed setting [6]. Its adverse effect on making cytopenias are also responsible of this condition. NF-κB pathway inhibitors such as bortezomib also cause cytopenies and decrease T cell proliferation, decrease the number and function of NK and T cells, inhibit the function and viability of dendritic cells, and alter cytokine secretion [6]. Herpes simplex and Varicella zoster virus activations are highly possible with bortezomib, but opportunistic actinomycoses infections such as *nocardia* are unusual, but they can be seen especially in the setting of lymphopenia [8,9]. Carfilzomib is also a novel and irreversible proteasome inhibitor with a sustained and specific action; and although the prevalence of pulmonary nocardiosis associated with carfilzomib is not known yet, it is reported, therefore it must be considered [10]. In our cases, all of the patients were above 65 years old, had a nonspecific cough complaint, they were all relapsed cases and have imid-based therapies, proteasome inhibitors (bortezomib), dexamethasone usage and stem cell transplantation histories in common. Two of our cases seem to have an adequate lymphocyte number, but the lymphocyte counts should be monitored closely because undulations may occur and the function is also affected by these therapies rather than the count itself. By considering the opportunistic infections, the necessary microbiologic and radiologic examinations were performed and early intervention with appropriate antibacterial treatment could be done. They received a prolonged course of antibacterial therapy due to their antibiograms and current treatment recommendations (Carbapenem and TMP/SMX combination and discharged with oral TMP/SMX therapy).

Table 1. Description of the general features of the studied cases (3)

<table>
<thead>
<tr>
<th>General features of the cases</th>
<th>Case-1</th>
<th>Case-2</th>
<th>Case-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>66</td>
<td>71</td>
<td>72</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Neutrophile count (2000-7000/mkrl)</td>
<td>7200</td>
<td>7060</td>
<td>4160</td>
</tr>
<tr>
<td>Lymphocyte Count (800-4000/mkrl)</td>
<td>1290</td>
<td>2300</td>
<td>520</td>
</tr>
<tr>
<td>Monocyte Count (120-1200/mkrl)</td>
<td>1760</td>
<td>450</td>
<td>680</td>
</tr>
<tr>
<td>Myeloma Type</td>
<td>Ig G kappa</td>
<td>IgG kappa</td>
<td>IgG kappa</td>
</tr>
<tr>
<td>Previous Treatment</td>
<td>Autologous SCT 4 years ago Lenalidomide-Dexamethasone</td>
<td>Autologous SCT 5 and 12 years ago Bortezomibe-Thalidomide-Dexamethasone</td>
<td>Autologous SCT 4 years ago Bortezomibe-Thalidomide-Dexamethasone</td>
</tr>
<tr>
<td>Recent Treatment Before Nocardiosis</td>
<td>Bortezomibe</td>
<td>Pomalidomide</td>
<td>Bortezomibe-Thalidomide-Dexamethasone</td>
</tr>
</tbody>
</table>
Case 1: A mass like infiltration at right lung superior lobe posterior segment suggesting Nocardia and after 2 months following the treatment, the regression of the infiltration.

Case 2: A 7x6x6 cm diameter sized mass like infiltration which also contains cavity at superior apical location of the right lung and 6 months later control CT shows formation of a bigger cavity but regression of the infiltration.

Case 3: A 4 cm diameter sized collapse-consolidation field which contains cavity fully filled with liquid at superior lobe posterior and inferior lobe superior segment of the right lung and one month later regression of the consolidation field.
Picture 4. Case-1, Colony image of nocardia at Blood-Sheep agar

Picture 5. Case-2, Acid-fast stain of sputum, branched bacilli image
6. CONCLUSION

For MM patients, especially for particular settings, it is prudent to follow the lymphocyte count closely and to keep in mind that kind of rare microorganisms like *nocardia* for the early intervention of appropriate antibacterial therapy.

CONSENT

As per international standard, patient’s written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard, ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

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