Reminder of important clinical lesson

Nocardiosis in a patient with rheumatoid arthritis treated with rituximab and a summary of reported cases

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Summary

Rituximab is a B-cell-depleting monoclonal anti-CD20 antibody. It is widely used in haematology and rheumatology. However, usage of rituximab in immunosuppressed patient has been associated with various opportunistic infections. The authors reported a case of refractory rheumatoid arthritis treated with rituximab, which later presented with non-resolving pneumonia with pulmonary nodule. Percutaneous computer tomogram guided lung biopsy was arranged to confirm the suspicion of tuberculosis, but did not yield conclusive results. Later, she presented left-chest abscess and underwent incision and drainage. The pus culture and sensitivity confirmed pulmonary nocardiosis with chest wall dissemination. She was treated with 2-week course of trimethoprim sulfamethoxazole and responded. The authors also reviewed published cases of nocardiosis post-rituximab.

BACKGROUND

The usage of rituximab in this patient had rendered her severely immunocompromised allowing the emergence of nocardia. In this era of biologics, all patients should have a sensible balance of risk and benefit.

CASE PRESENTATION

We report a case of a 58-year-old retired lady, with a history of long-standing rheumatoid arthritis and who was managed previously on multiple immunosuppressive therapies. Her other co-morbidities include lung fibrosis, bronchial asthma, steroid-induced diabetes mellitus and Cushing's syndrome, trigeminal neuralgia, dyslipidaemia and carpal-tunnel syndrome.

She was given various types of disease-modifying anti-rheumatic medications; however, the disease remained uncontrolled. Despite the administration of cyclosporine, azathioprine and low-dose corticosteroid, her disease was still refractory to treatment. Rituximab was considered for administration, in view of the failure of treatment with the use of disease-modifying agent and vasculitis. As the disease became incapacitating, rendering the patient bedbound, rituximab had to be given.

Two weeks after the second dose of the rituximab, she presented with fever, chest pain and dyspnoea. Chest radiograph revealed a left lower zone consolidation, and she was treated for nosocomial pneumonia subsequently. As she was bedbound and electrocardiogram showed changes suspicious of pulmonary embolism, CT pulmonary angiogram was performed. Alarming, it showed an intraparenchymal speculated mass in the subpleural region at the left upper lobe, measuring 3.3×2.7×2.5 cm, with central necrosis. Subsequently, a percutaneous, CT-guided, lung biopsy was performed with an 18G trucut biopsy needle. Histopathology examination of the lung nodule only showed interstitial pneumonia-like changes with fibrosis. No feature of

granulomatous disease or fungal infection was noted in the study.

She presented again with pneumonia a month later. The chest radiogram showed similar changes. The blood culture grew *Candida albicans*, and IV fluconazole was started. However, the fever did not resolve, and she was given multiple courses of antibiotics. Subsequently, she complained of persistent left-sided chest pain, along with worsening dyspnoea. Examination revealed a tender and swollen left breast. Ultrasound of the left breast showed non-liquefied abscess. CT scan showed multiseptated intramuscular abscess with pockets of air and poorly delineated left pectoralis major muscle. The previously seen pulmonary nodule had increased in size. Incision and drainage of left breast was arranged and 800 cc of pus was drained. The fungal culture and sensitivity showed a partially acid-fast organism with branching filaments, which was confirmed as *Nocardia* sp spp. She was treated with co-trimoxazole, for a period of 2 weeks. She responded to the medication and the fever decreased, with noticeable improvement in her condition. The wound healed with secondary healing. Histopathological examination of the left breast tissue showed chronic granulomatous inflammatory lesions.

INVESTIGATIONS

High-resolution CT Thorax showed 1A-intraparenchymal speculated mass seen in the subpleural region at the left upper lobe before the lung biopsy. 1B-Pectoralis major abscess with intraparenchymal lesion along the needling tract (figure 1).

Fungal culture and sensitivity revealed nocardiosis spp.

DIFFERENTIAL DIAGNOSIS

Mycobacterium spp., *Staphylococcus aureus*, *Bacteroides* spp. infections, Breast carcinoma.

Figure 1 (A) Intraparenchymal speculated mass seen in the subpleural region at the left upper lobe before the lung biopsy. (B) Pectoralis major abscess with intraparenchymal lesion along the needling tract.

Reference	Age and Sex	Underlying Disease	System involved	Culture Results	Usage of Other Immunosuppression	Treatment	Outcome
Ansari et al ⁹	58 y, male	CLL NSCLC	Pulmonary	<i>N. veteran</i> , <i>N. nova</i>	Fludarabine, cyclophosphamide	TMP—SMX, voriconazole, azithromycin, piperacillin/tazobactam and valganciclovir	Improved
Flohr et al ¹⁰	45 y, female	LRRT	Pulmonary	<i>N. nova</i>	ATG, IVIG, TAC, ATG, WPE, MMF, Steroid	TMP-SMX	Improved
Kundra et al ¹¹	68 y, male	NHL, DM	Cerebral abscess	<i>N. brasiliensis</i>	Radiation and chemotherapy	Not stated	Not stated

NA, not available; CLL, Chronic Lymphocytic Leukaemia; NSCLC, Non-small cell lung cancer; TMP—SMX, trimethoprim—sulfamethoxazole; LRRT, living related renal transplant; ATG, antithymocyte globulin; IVIG, Intravenous immunoglobulin; TAC, tacrolimus; WPE, whole plasma exchange; MMF, mycophenolate mofetil; NHL, Non-Hodgkin's lymphoma; DM, Diabetes Mellitus

Figure 2 Summary of published Cases of Nocardiosis Post-Rituximab.

TREATMENT

She was treated with 2 weeks of intravenous TMP-SMX and later continued with the oral form.

OUTCOME AND FOLLOW-UP

She was seen in the clinic 2 weeks later, but she was subsequently admitted for severe drug reaction. She was then discharged well.

DISCUSSION

Deciding on which are the best investigations and treatment modalities is a difficult task. We described a case of

pulmonary nocardiosis with needle tract seeding to the pectoralis major muscle after receiving rituximab for refractory rheumatoid arthritis.

Rituximab, a B-cell-depleting monoclonal anti-CD20 antibody, was approved by the Malaysian Drug agency in 2007. There are limited local data on the side effect of rituximab. REFLEX¹ has shown that serious infections occurred in only 5.2% of the patient population who received rituximab, compare to 3.7% of those in the placebo category. However, there was no report on occurrence of opportunistic infections during the 24 weeks of the study. According to Salliot *et al*,² respiratory tract bacterial infection is the main mode of serious infection, as illustrated in our case. The

meta-analysis also did not show significant occurrence of opportunistic infections.

Nocardia sp., is a Gram-positive bacillus, aerobic actinomycetes in the genus *Nocardia* sp., with partial acid-fastness. Partial acid-fastness is a unique characteristic of *Nocardia* sp. that is not exhibited by other actinomycetes. There are more than 50 known species, and more than 50% of them cause infections in humans.³ However, *Nocardia* sp. *asteroids* are known to cause infection predominantly in humans.⁴ It is an opportunistic infection in immunocompromised patients. Its main route of acquisition is through aerosol, which explains why lungs are a primary site of infection in more than two-thirds of cases reported.^{5 6} Other modes of infections are ingestion of contaminated food products and direct inoculation from trauma. In the case of our patient, she possibly acquired the infection through aerosol route, which later disseminated to the chest wall after needle lung biopsy.

Nocardiosis occurs in people with depressed cellular immunity. The risk factors for acquisition of the disease are usage of long-term glucocorticoids, immunosuppressive therapy, underlying lung disease, lymphoproliferative diseases, transplantation, and AIDS. It is possible that our patient had already acquired the nocardiosis prior to initiation of rituximab. The immunosuppressive effects of rituximab had caused a rapid, accelerated growth of nocardiosis. The haematological side effects of rituximab also lead to T-cell dysfunction via bone marrow, which included hypoplasia, lymphopenia, neutropenia and leucopenia.

During our literature search, we have noted that there were a few reported cases of nocardiosis post-rituximab. From this search, we also noted that there were two reported cases with pulmonary nocardiosis as in the case of our patient. In addition, there were also two cases of lymphoproliferative disease which may contribute to lymphocytes dysfunction leading the nocardiosis. A wide variety of immunosuppressant therapy had been given to the three patients as stated in figure 2. From these cases, the patient's underlying immunosuppression from the underlying co-morbidity posed a confounding factor for the development of nocardiosis. We can suppose that the more immunosuppressed the patient is, the higher the risk of acquiring nocardiosis.

The treatment of choice of *Nocardia* sp. infections is Trimethoprim-sulfamethoxazole. As we can see from the

list of reported cases, two responded to TMP-SMX, as was the case with our patient.

The lesson to learn here is that opportunistic infection should always be anticipated in an immunocompromised host. The delay in diagnosing a dire infection can render a patient in danger. Thus, the benefit versus the complication of treatment or investigation should always be considered carefully.

Learning points

- ▶ Rituximab is a potent immunosuppressive agent.
- ▶ Opportunistic infections may appear with the use of biologic therapy.
- ▶ A close surveillance of infection must always be done in a patient receiving immunosuppressive therapy.

Competing interests None.

Patient consent Obtained.

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Ngiu CS, Said MSM, Periyasamy P, Low SF. Nocardiosis in a patient with rheumatoid arthritis treated with rituximab and a summary of reported cases. *BMJ Case Reports* 2010;10.1136/bcr.11.2009.2421, date of publication

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