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Case Report

Association between nocardia farcinica opportunistic Infection and type 1 multiple endocrine neoplasia

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Abstract: Background: The global incidence of immunocompromised individuals has *increased* in recent decades; Many of these individuals are suffering from Nocardiosis. However, this is the first published report of *Nocardia* infection associated with Multiple Endocrine Neoplasia Type 1 (MEN-1). In this article, a case of Nocardial brain abscess is presented. Clinical presentation: The patient is a 31-years-old male presented with MEN-1. The patient was then diagnosed with a *Nocardia farcinica* infection according to visual inspection and diagnostic of skin pustules, bilateral ventricle drainage culture, and lung biopsy. The patient soon developed pneumonia, as well as skin and cerebral infections. A diffuse brain abscess was detected by intracranial CT. The diffuse brain abscess was aspirated through two burr holes in the skull. The patient was treated with the following medication, Amikacin, Imipenem, compound Sulfamethoxazole, and Linezolid for 3 weeks. Although the antimicrobial therapy is often effective and appropriate according to the guidelines for treating Nocardial infection, In this case, the patient died. Conclusion: Nocardial brain abscess is a rare central nervous system (CNS) infection which may differ from other brain lesions. Treatments include surgical management and long-term antibiotic therapy. The timely diagnosis for MEN-1 is imperative, and the aggressive preventative treatment for potential CNS involvement is a key factor. This important strategy will help to avoid the "fungi-like" filamentous growth of *Nocardia* sp.

Keywords: Brain abscess, nocardial infection, MEN-1, immunosuppression, opportunistic infection

Introduction

Nocardiosis has recently become a significant opportunistic infection [1], However, no previous cases of *Nocardia* infection associated with Multiple Endocrine Neoplasia Type 1 (MEN-1) have been reported. MEN-1 is a rare autosomal dominant genetic disease, caused by mutations in the tumor suppressor gene MEN-1. Clinical manifestations of MEN-1 are determined by the locations of tumors in the endocrine system, and by the hormones they secrete. The glands and organs that are most commonly affected by MEN-1 are the parathyroid, pituitary and adrenal glands and the pancreas. MEN-1 is usually associated with a marked increase in the glucocorticoid secretion, then leading to immunosuppression [2].

Nocardia can be identified with the aid of Gram and modified Kinyoun staining. CNS involvement constitutes the most severe form of Nocardiosis. In comparison with other bacterial brain abscesses, those due to *Norcaria* are difficult to diagnose clinically [3]. Few cases with CNS involvement have been reported and there are no publications on the optimal therapeutic regimen. Herein we describe the clinical course, radiological findings, and management of a case.

Case presentation

The patient, a 31-year-old Chinese male, first presented to out hospital on January 26, 2015, with a one-month history of edema of the face and lower limbs. This was associated with an

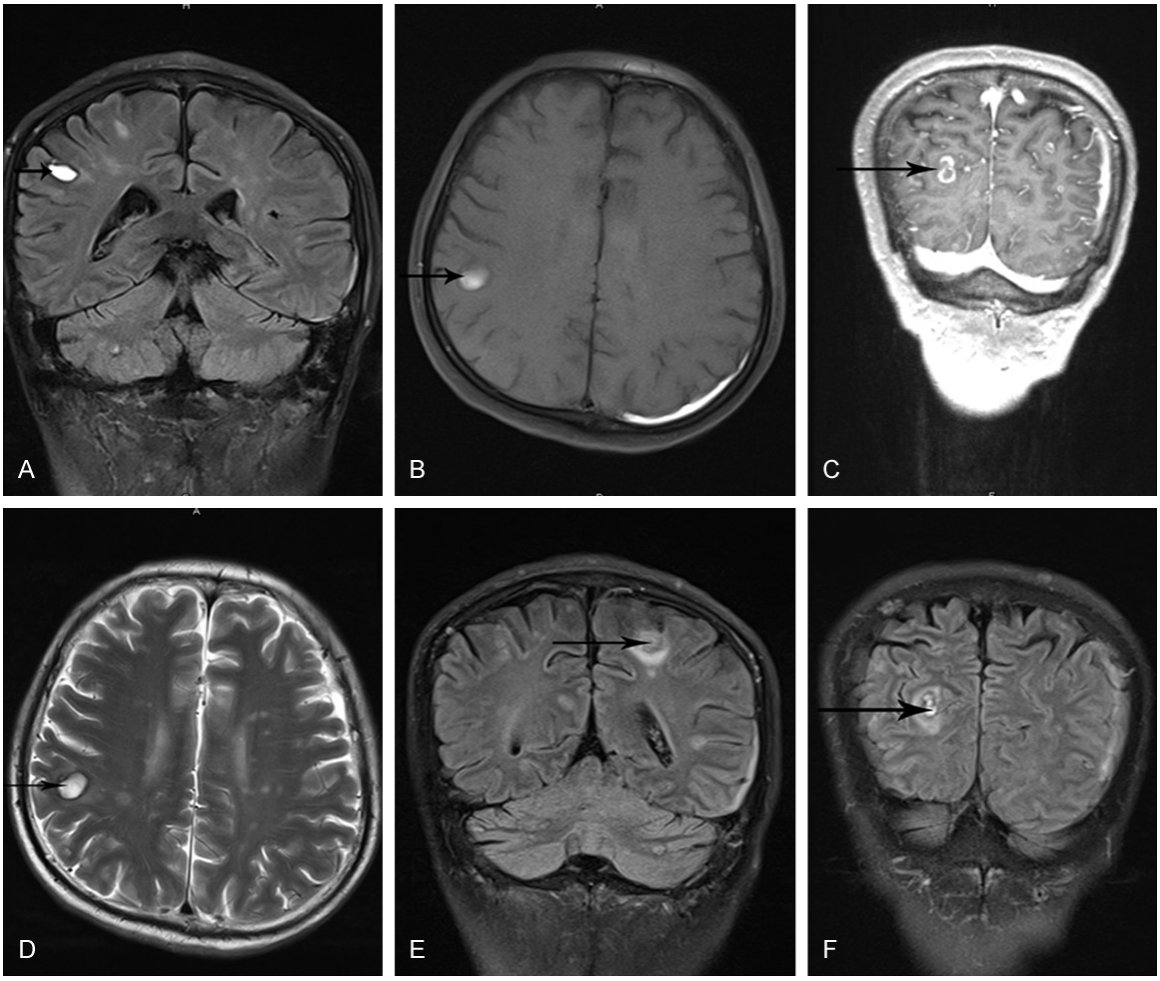

Figure 1. Intracranial MRI scan with enhancement, February 5, 2015. A-F. Show ring enhancement of the right frontal lobe. The left pituitary gland is ca 4 × 2 mm, with relatively low contrast enhancement; a pituitary adenoma was considered.

eruption of acne on the torso (chest and back), significant weight gain (4 kg over 1 month), and a significant decrease in libido. The patient had developed hemoptysis two days before his admission. He had a history of appendectomy 24 years ago. There was no history of tuberculosis or type 2 diabetes and no history of using steroids, traditional homeopathic remedies or herbal medications.

On examination, the patient weighed 76 kg, was 170 cm tall, had a body mass index (BMI) of 26.3 kg/m^2, the patient's waist and hip circumferences were 91.5 and 97 cm, respectively. His blood pressure and pulse presented at 146/97 mmHg and 86 beats/min. The patient had moderate edema in the face and lower extremities. He had central obesity. He was mildly anemic, with no goiter or clinically palpable lymph nodes. There was no gynecomastia, striae, or evidence of pruritus. His visual fields were normal and there was no papilledema. Other physical findings were unremarkable.

Initial laboratory results showed low levels of thyroid stimulating hormone (TSH) (0.119 μIU/ml, reference range 0.27-4.2), free triiodothyronine (FT3) (2.18 pg/ml, reference range 2.3-4.2), free thyroxine (FT4) (0.82 ng/dl, reference range 0.89-1.76), total triiodothyronine (TT3) (0.59 ng/ml, reference range 0.6-1.81) and testosterone (0.82 ng/ml, reference range 14-25.4). The patient's parathyroid hormone level was high at 1015.10 pg/ml (reference range 230-630 ng/l). Screening for Cushing's syndrome was done at a local hospital and had revealed that the patient 24-hour urine cortisol was significantly elevated at 534.05

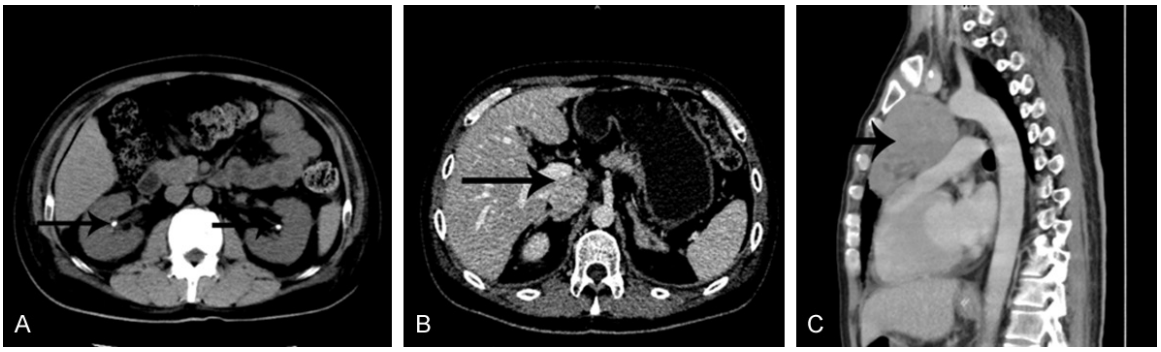

Figure 2. CT scan with enhancement, of lower and upper abdomen and chest, February 5, 2015. A: Multiple small stones are visible in both kidneys; B: Two nodules are visible in the pancreatic head region; there is bilateral adrenal gland enlargement, with the possibility of hyperplasia; C: Upper mediastinal mass, possibly an invasive thymoma.

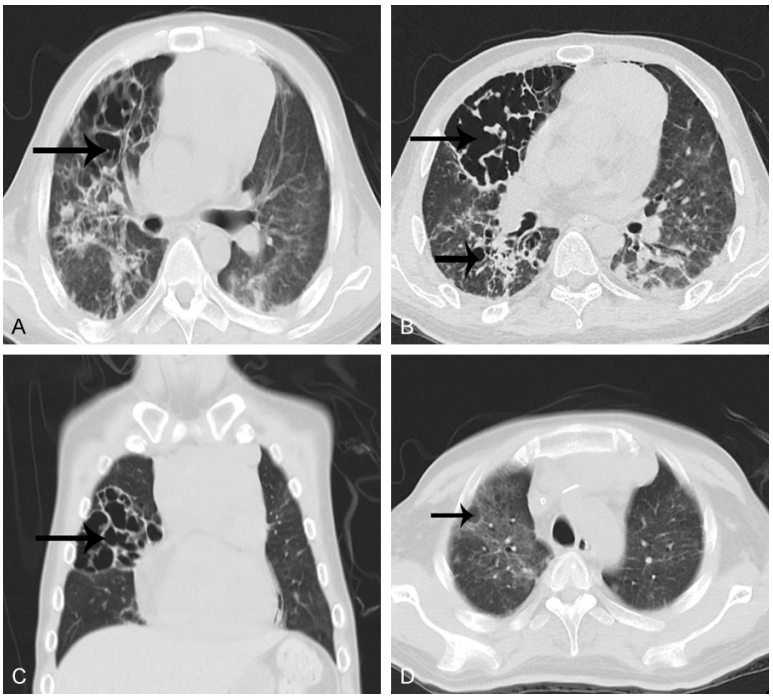

Figure 3. Chest CT scan, February 9, 2015. A-D. Show small nodules and air sacs are visible in both lungs.

nmol/24 h (reference range 130-304) and that the patient's adrenocorticotropic hormone (ACTH) levels were elevated at both 8:00 am and midnight, at levels of 22.5 pg/ml (reference range, 2.2-22.0) and 9.7 pg/ml (reference range 1.1-4.4) respectively. Moreover, cortisol was not inhibited by either low or high dose dexamethasone. This marked increase of glucocorticoid secretion is known to be associated with immunosuppression.

MEN1 gene mutations were found in both the patient and his father.

These comprised heterozygous *C→A* mutations located at the 7,984th nucleotide, resulted in a termination codon UAA, and the truncation of menin. This is known to be associated with the MEN1 phenotype. And his fathers' diagnosis, revealed MEN1 with a germline deletion in exon 6 and a c.492 deletion C, p.Phe158LeufsX53. The findingsin the patient's mother and other relatives were normal. Both the history and the laboratory findings were consistent with MEN-1.

On February 5, 2015, an intracranial MRI scan with enhancement showed a pituitary adenoma was suspected (**Figure 1**). On February 5, 2015, a contrast enhanced MRI scan showed a relatively low-contrast lesion on the left side of the pituitary gland measuring approximately 4 × 2 mm (**Figure 2**). A contrast-enhanced CT of the lower and upper abdomen and chest showed lesions in the kidneys, pancreas, bilateral adrenal glands and (**Figure 3**). Treatment with the antibiotics Imipenem and Moxifloxacin was started. On February 15, 2015, his chest, back, and limbs were found to be covered with small pustules, of which culture was taken and yielded gram-positive filamentous bacilli, identified as *Nocardia farcinica*. Lung biopsy specimens were also obtained

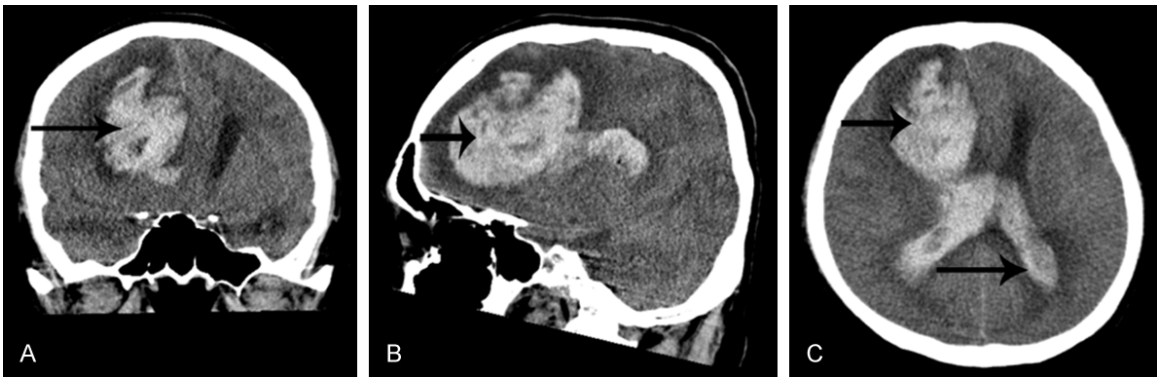

Figure 4. Intracranial CT scan, March 3, 2015. A-C. Show a hemorrhage in the right frontal lobe, breaking into the body of the right ventricle, the third ventricle, the left lateral ventricle angle, the mid-brain aqueduct and the fourth ventricle. A diffuse brain abscess is seen.

and the histological examination also revealed the presence of *Nocardia farcinica.* The antibiotic regimen was changed to Piperacillin-Tazobactam, Linezolid, Amikacin, and compound Sulfamethoxazole.

On February 20, 2015, the patient developed a productive cough and his blood oxygen saturations fell. He was intubated and artificial ventilation commenced. Chest X-ray and CT showed evidence of a pulmonary infection (**Figure 3**).

On March 3, 2015, an intracranial CT showed a hemorrhage in the right frontal lobe, breaking into the body of the right ventricle, the third ventricle, the left lateral ventricular angle, the mid-brain aqueduct and the fourth ventricle. A diffuse brain abscess was also seen (**Figure 4**). We undertook immediate bilateral ventricular drainage under general anesthesia. The drainage fluid was cultured and infection with *Nocardia farcinica* was confirmed. Mannitol dehydration treatment was given. However, the patient's neurological status did not improve and respiratory failure developed.

On March 3, 2015, the antibiotic treatment was modified to compound sulfamethoxazole, linezolid, Meropenem, and minocycline. Later that day, the patient became pulseless and hypotensive. Due to a DNAR status (no CPR and no cardioversion), the patient died shortly afterward.

Discussion

Our case report is the first to document Nocardial infection in a patient with MEN-1. Nocardiosis is typically an opportunistic infection in immunosuppressed patients, such as individuals with HIV infection, severe Systemic Lupus Erythematosus (SLE) or long-term use of Corticosteroids.

The patient's thyroid axis, gonadal axis, and the endocrine system had all been inhibited by negative feedback, with markedly increased levels of ACTH.

Despite using the appropriate antimicrobial therapy, the bacteria crossed the blood-brain barrier, growing in a filamentous manner along the blood vessel walls and rendering them fragile. This subsequently leads to cerebral hemorrhage and death.

Elevated ACTH, as seen in MEN-1, usually leads to a marked increase in glucocorticoid secretion. Opportunistic infections are more likely found, under these conditions, because of the suppression of alveolar macrophages and the mobilization of neutrophils to areas of increased glucocorticoid secretion [4]. The high mortality rate from opportunistic infection in MEN-1 may be due to hypercortisolism, which can mask the signs and/or symptoms of infection and delay diagnosis [5].

This case highlights the importance of considering *Nocardia* sp. as a causative agent for intracranial hypertension in patients diagnosed with MEN-1.

The site of infection and the host's general health can determine the prognosis of a Nocardial infection [6]. Brain abscesses make

up approximately 2% of *Nocardia* sp. Infections [7]. The Morbidity and the mortality rate are high for opportunistic infections in MEN-1 [1, 8]. The manifestation of the brain abscess seen here is very similar to that of many tumors [9, 10], or that of a cerebral infarction [11].

Numerous previous studies have highlighted the importance of timely diagnosis [6, 12-14]. Clinical practice guidelines for MEN-1 [15] recommend that it should be treated by a multidisciplinary team and that patients and their families should participate in decision-making about treatment. CNS involvement is seen in approximately 40% of systemic Nocardiosis [16]. Sulfonamides are the first-line treatment. Mortality rates for Nocardial cerebral abscesses are now likely to be lower than before, due to the advancements of MRI and rapid laboratory identification of pathogens.

However, timely diagnosis and preventative treatment may still be the most important defense strategy against craniocerebral infections by *Nocardia* sp., which have a "fungi-like" filamentous growth. Stronger investigative measures are required, both for *Nocardia* sp. infection and for CNS involvement, in any potentially immunosuppressed patient, no matter the causes of the immunosuppression. Including but not limited to long-term corticosteroid use, HIV infection, infectious endocarditis, SLE or MEN-1.

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Disclosure of conflict of interest

None.

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