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Iatrogenic Primary Hypothyroidism Associated With Sulfamethoxazole-Trimethoprim Treatment of Nocardiosis in a Cat

Deborah Alexander[1] | Gustavo C. Cobucci[2] | Cassia C. da Motta[3] | Gabriela de C. Cid[4] | Lana S. Belizzi[1] | Amanda C. de Jesus[1] | Heloisa J. Souza[4] | Mark E. Peterson[5]

[1]Vida Felina Veterinary Clinic, Rio de Janeiro, Rio de Janeiro, Brazil | [2]GammaVet, Rio de Janeiro, Rio de Janeiro, Brazil | [3]TECSA Laboratory, Rio de Janeiro, Rio de Janeiro, Brazil | [4]Universidade Federal Rural do Rio de Janeiro, Seropédica, Rio de Janeiro, Brazil | [5]Animal Endocrine Clinic, New York, New York, USA

Correspondence: Mark E. Peterson (drpeterson@animalendocrine.com)

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ABSTRACT

A 9-year-old mixed breed cat with a history of recurrent ulcerated skin lesions was diagnosed with nocardiosis. Three months after initiating potentiated sulfonamide treatment, the cat developed goitrous hypothyroidism, characterized by palpable enlargement of both thyroid lobes, low serum concentrations of total thyroxine (T4) and free thyroxine (fT4), and high serum thyroid-stimulating hormone (TSH) concentration. Thyroid scintigraphy identified symmetrical enlargement of both thyroid lobes, with increased radionuclide (^{99m}Tc-pertechnetate) uptake. Upon discontinuation of trimethoprim-sulfa, serum concentrations of T4, fT4, and TSH returned to normal, confirming the diagnosis of iatrogenic, drug-induced thyroid dyshormonogenesis leading to hypothyroidism. A skin lesion was surgically removed, and microscopy disclosed branched filaments along with characteristic Gram-positive coccobacilli and Splendore-Hoeppli phenomenon. Using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS), the clinical isolate was identified as *Nocardia puris*.

1 | Introduction

Nocardia spp. are Gram-positive filamentous branching bacilli, classified within the group of aerobic actinomycetes. As saprophytic bacteria, they are commonly found in soil, water, and decomposing organic matter [1–3].

Nocardiosis is considered a rare disease in both companion animals and humans. However, *Nocardia* spp. can cause severe and refractory infections, particularly in animals [1, 3–6]. Diagnosing *Nocardia* spp. infections is challenging because of their fastidious nature, as their growth can be masked by other microorganisms, and the availability of diagnostic tests to differentiate *Nocardia*, *Mycobacterium*, and *Actinomyces* species is limited [2].

Treatment of cutaneous-subcutaneous nocardiosis typically involves the use of antimicrobials combined with surgical debridement [1, 3]. Trimethoprim-sulfamethoxazole (TMP-SMX) is a broad-spectrum antibacterial and antiprotozoal agent, regarded as the first-line treatment for *Nocardia* infections [2, 7].

Abbreviations: fT4, free T4; LEHR, low energy high resolution; L-T4, levothyroxine sodium; MALDI-TOF MS, matrix-absorption laser desorption ionization-time-of-flight mass spectrometry; OMP-SDX, ormetoprim-sulfadimethoxine; T4, thyroxine; TMP-SMX, trimethoprim-sulfamethoxazole; TSH, thyroid-stimulating hormone.

Potentiated sulfonamides, such as TMP-SMX, can interfere with thyroid function in species susceptible to their effects. In humans, these drugs may induce thyroid hormonal imbalances [8]. In dogs and rats, potentiated sulfonamides are known to cause goitrogenic hypothyroidism [9–16]. Recently, sulfonamide-associated hypothyroidism also was reported in a cat [17].

2 | Case Description

A 9-year-old, male neutered, mixed breed cat weighing 5.45 kg was presented to the hospital for evaluation of a 4-year history of recurrent ulcerated skin lesions on the abdomen and right side of the thorax. Medical history determined that the cat had been treated with antifungals (itraconazole), antibiotics (marbofloxacin, spiramycin and metronidazole, amoxicillin), anti-inflammatory drugs (meloxicam), and corticosteroids (prednisolone). On some occasions, the cat responded to treatment, remaining free of wounds for long periods. However, over the past 8 months, the lesions had progressively worsened. Two months before presentation, cytology examinations of an ulcerated lesion and fungal and bacterial cultures (swab of exudate) were performed. Cytology identified filamentous branching, partially acid-fast organisms, morphologically compatible with *Nocardia* spp. and *Actinomyces* spp. Microbiological cultures were negative for fungi, *Nocardia* spp., and *Mycobacterium* spp.

At the time of presentation (Day 0), the cat had been receiving ormetoprim-sulfadimethoxine (OMP-SDX) 21 mg/kg PO q24h for 2 months. On physical examination, the cat was lethargic, with a rectal temperature of 40.2°C. Thyroid lobes were not palpable. Skin inspection identified multiple fistulated lesions with bloody exudate located in the middle epigastric region and right lateral thorax, in addition to a nodule (4.0 × 2.0 cm) located caudal to the fistulas in this region (Figure 1A,B). The exudate contained small, yellowish-white granules visible macroscopically. Blood samples were collected for CBC, serum biochemical profile, and feline immunodeficiency virus (FIV) and feline leukemia virus (FeLV) testing. Mild neutrophilic leukocytosis was observed (14 000 neutrophils/μL; reference interval [RI], 2500–12 500 neutrophils/μL). Real-time PCR tests for FIV and FeLV were negative. The owner declined biopsy or additional diagnostic testing. Differential diagnoses included nocardiosis, non-tuberculous cutaneous mycobacteriosis, and actinomycosis. The tablet form of OMP-SDX was replaced by an injectable form of trimethoprim-sulfamethoxazole (TMP-SFX, 18 mg/kg SC q12h). Treatment was complemented with folic acid (1 mg PO q24h), meloxicam (0.05 mg/kg PO q24h for 3 days), and dipyrone (25 mg/kg PO q24h for 3 days).

Nine days (Day 9) after the initial presentation, the cat was re-evaluated and showed considerable improvement in the skin lesions on the ventral abdomen. However, the nodule on the right side of the thorax had ulcerated, with drainage of purulent discharge and the presence of sulfur granules (i.e., aggregates of bacteria microcolonies surrounded by eosinophilic material) on cytology [1–4, 18].

The cat was more active and eating well, with a rectal temperature of 40.7°C. The CBC showed neutrophilic leukocytosis with a left shift (39 032 neutrophils/μL and 1428 bands/μL). Chest radiography showed no abnormalities. The dosage of TMP-SFX was increased (25 mg/kg SC q12h), and marbofloxacin (2.75 mg/kg PO q24h) was added. Thirty-five days after the initial visit (Day 35), the cat was more active without fever, and skin lesions were completely healed. The CBC and serum biochemical profile were normal.

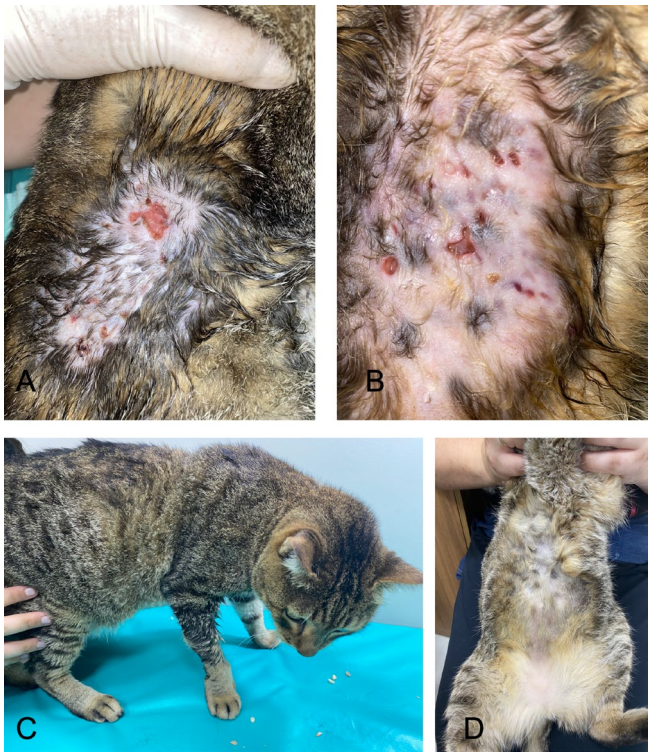

FIGURE 1 | Ulcerated and nodular lesions observed in a 9-year-old male neutered mixed-breed cat with nocardiosis. (A) Lesions on the right side of the thorax; (B) Lesions on the ventral abdomen after shaving and antisepsis; (C, D) The cat was reexamined on Day 71, with complete resolution of the skin lesions located in the right lateral region of the thorax and ventral abdomen.

A month later (Day 71), the cat was alert and active, with a normal appetite and no skin lesions (Figure 1C,D). The cat now weighed 5.8 kg, a gain of 0.35 kg. Although the cat was clinically normal, antimicrobial treatment was continued because of the suspicion of residual nocardiosis. On Day 92, both thyroid lobes were now palpable on physical examination. Serum concentrations of total thyroxine (T4) and free thyroxine (fT4) were measured by chemiluminescent enzyme immunoassay and found to be low (T4, 0.6 μg/dL; RI, 0.8–4.7 μg/dL; fT4, < 0.3 ng/mL; RI, 0.7–2.6 ng/dL). Serum thyroid-stimulating hormone (TSH) concentration, measured by chemiluminescent enzyme immunoassay, was very high (> 12.0 ng/mL; RI, 0.03–0.38 ng/mL). To confirm the results, another blood sample was collected 1 week later (Day 99), and similar results were obtained (T4, 0.5 μg/dL; fT4, < 0.3 ng/mL; TSH > 12.0 ng/mL). Thyroid scintigraphy was scheduled to further evaluate the cat's hypothyroidism.

On Day 108, all medications (TMP-SFX and marbofloxacin) were discontinued, and thyroid scintigraphy was performed, as previously described [19–21]. Scintigraphy was performed 60 min after the SC administration of 5 mCi of technetium pertechnetate ($^{99m}TcO_4^-$). The cat was manually restrained, with the gamma

camera equipped with the low energy high resolution (LEHR) collimator positioned ventral to the cat. Two images were obtained with the cat in sternal recumbency, adjusted for a time of 60 s and maximum number of 350,000 counts, respectively [19, 20]. The third image was obtained with the cat in right lateral recumbency and adjusted for a time of 30 s. Then, the LEHR collimator was replaced with a pin-hole collimator and, again, with the cat in sternal recumbency, an image was acquired for 60 s (Figure 2). Image analysis was performed using digital imaging and communications in medicine (DICOM) image processing software (Genie Xeleris, GE Medical Systems). The examination followed standard 6.12 of the National Nuclear Energy Commission, which describes the safety and radiation protection requirements for veterinary nuclear medicine services [22].

On evaluation of the cat's thyroid scan, the right and left thyroid lobes appeared symmetrically enlarged and active, which was verified by confirming high results for both thyroid volume and $^{99m}TcO_4^-$ uptake. The percent thyroidal uptake of the injected sodium ^{99m}Tc-pertechnetate was very high at 8.87% (RI, 0.05%–0.80%). The thyroid/salivary ratio was high in both thyroid lobes (T/S ratios, 3.69 and 3.66 in the right and left lobes, respectively; RI 0.5–1.5). These scintigraphic results, together with the low serum T4 and fT4 concentrations and high TSH concentrations, were diagnostic for hypothyroidism caused by dyshormonogenesis [21, 23].

Two months after the withdrawal of TMP-SFX, the cat again was evaluated (Day 155). On physical examination, the thyroid lobes were still palpable. The cat was in good condition (body weight, 6.0 kg) and active, with no apparent skin lesions. The low serum T4 concentration had normalized, increasing from 0.6 to 2.0 μg/dL, and the high serum TSH also had normalized, decreasing from >12.0 to 0.07 ng/mL. Serum thyroid test results, before and after the withdrawal of TMP-SFX, supported the diagnosis of iatrogenic, drug-induced hypothyroidism associated with dyshormonogenesis caused by TMP-SFX [9, 12–14, 17].

On Day 217, the cat returned with an ulcerated lesion draining hemorrhagic fluid, measuring approximately 0.5 cm and located in the right scapular region. Doxycycline (10 mg/kg PO q24h) was initiated as antimicrobial treatment. Sixty days later (Day 272), this small ulcerated lesion evolved into a nodular ulcerated lesion measuring 5×4 cm. Another nodule measuring 7×4 cm was observed on the ventral abdomen. The cat was apathetic and febrile (40.2°C). Results of CBC, serum biochemical profile, and serum T4, fT4, and TSH concentrations (T4, 3.66 μg/dL; fT4, 1.5 ng/dL; and TSH, 0.09 ng/mL) showed no abnormalities. Cytology of an aspirate of the ulcerated lesion indicated pyogranulomatous inflammation. Filamentous bacterial organisms suspected to be *Actinomyces* or *Nocardia* were observed with Romanowsky staining. Culture was performed from a swab of exudative material from this lesion, but there was no fungal or bacterial growth. Given the worsening condition, a combination of TMP-SFX (19 mg/kg SC q24h) and marbofloxacin (2.75 mg/kg PO q24h) was restarted, with daily cleaning and mechanical protection of the wounds with a non-adherent dressing.

Twelve days after restarting treatment with TMP-SFX (Day 286), the lesion in the scapular region remained ulcerated (Figure 3A) and the nodule on the abdomen had fistulated and was draining a hemorrhagic exudate (Figure 3B). A CBC showed mature neutrophilia (43 896 neutrophils/μL). Although the serum T4 and TSH concentrations remained within RI, the serum T4 concentration had decreased into the low normal range (1.0 μg/dL) and serum TSH had increased into the high normal range (0.20 ng/mL).

At a follow-up visit 18 days later (Day 304), the cat appeared lethargic and depressed. However, the skin lesions had improved.

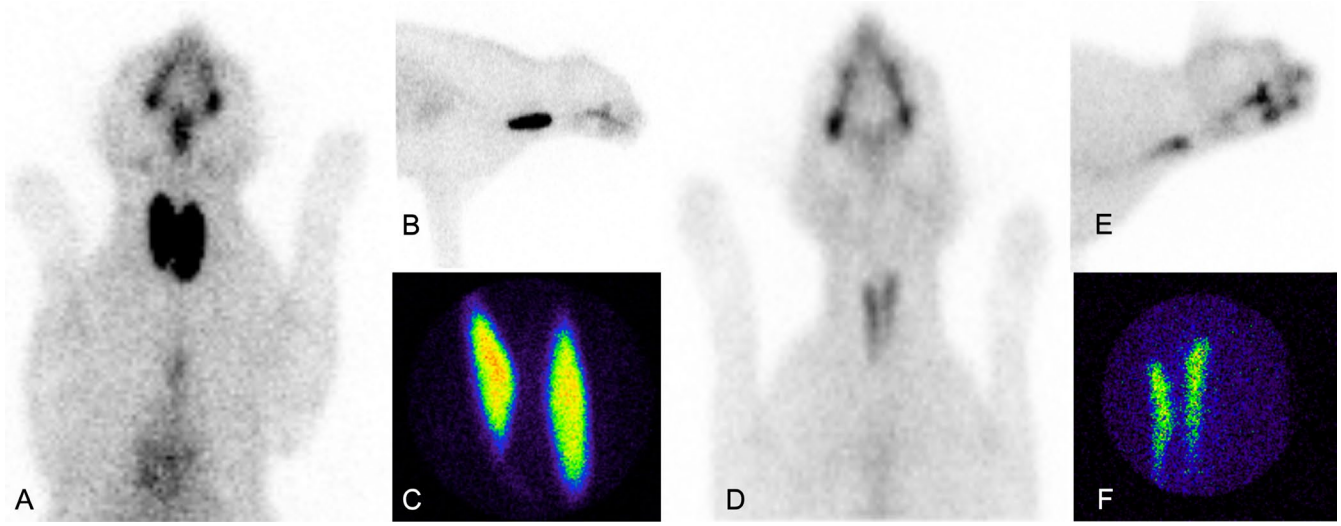

FIGURE 2 | Thyroid scintigraphic images of a cat diagnosed with sulfonamide-induced goitrous hypothyroidism, compared to an euthyroid cat. (A, B) Planar scintigraphy with LEHR collimator of our hypothyroid cat in ventral and lateral positions showing symmetrically large thyroid lobes and increased radiopharmaceutical uptake. (C) Scintigraphy of our hypothyroid cat using a pin-hole collimator also showing bilateral volume increase in thyroid lobes and increased radiopharmaceutical uptake. (D, E) Planar scintigraphy with LEHR collimator of a clinically normal euthyroid cat taken in ventral and lateral positions showing normal volume and radiopharmaceutical uptake (F) Scintigraphy performed with pin-hole collimator also showing normal volume and radiopharmaceutical uptake.

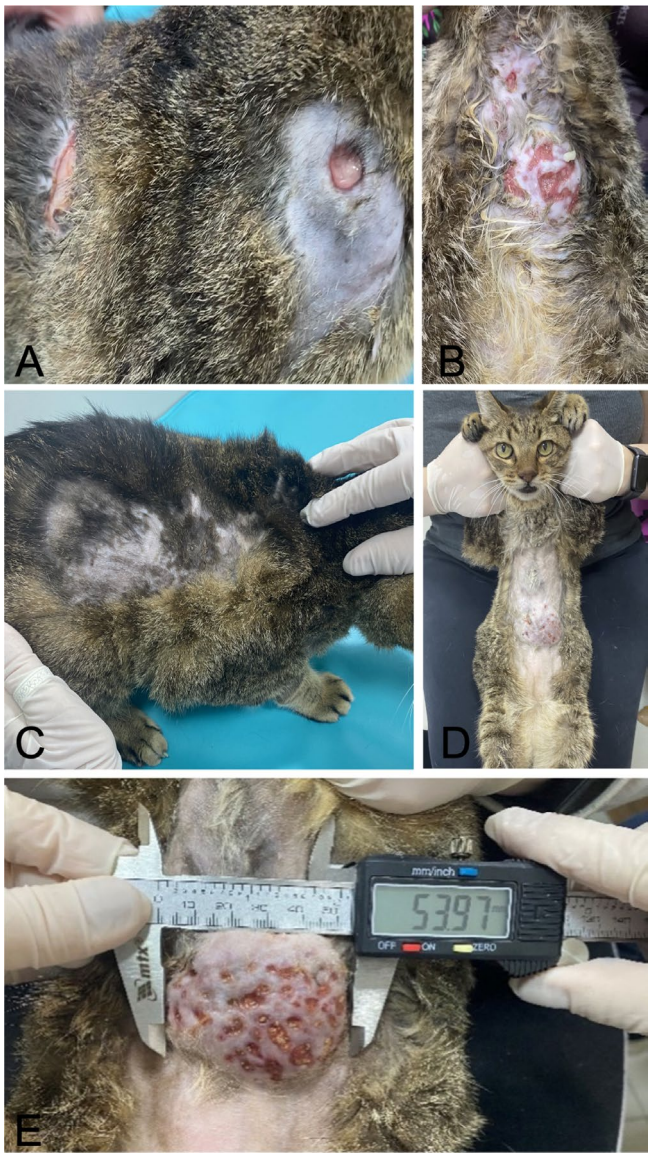

FIGURE 3 | Affected cat (Day 286) showing worsening of recurrent ulcerated nodular lesions in the right scapular region (A) and ventral abdomen (B). Same cat (Day 316) showing considerable improvement in recurrent ulcerated nodular lesions in the right scapular and lumbar region (C) and ventral abdomen (D). Same cat (Day 365) showing a well-circumscribed subcutaneous abdominal mass (approximately 5.4 cm diameter) with sinus tracts draining purulent exudate and yellowish-white granules (E).

Determination of serum thyroid hormone concentrations again indicated iatrogenic hypothyroidism, with a low T4 concentration (< 1.0 μg/dL) and a high serum TSH concentration (5.97 ng/mL). To treat recurrent hypothyroidism, levothyroxine sodium (12.5 μg/kg PO q12h) was started. After 30 days of levothyroxine (Day 350), serum concentrations of T4 and TSH again were within their respective RI (T4, 2.88 μg/dL; TSH, 0.16 ng/mL).

On Day 316, the skin lesions showed substantial improvement (Figure 3C,D). However, the cat had developed normocytic, normochromic (non-regenerative) anemia (hematocrit, 16%), requiring a blood transfusion. Treatment with TMP-SFX was continued, and marbofloxacin was replaced with clarithromycin (62.5 mg PO q24h). After this adjustment, the cat's clinical condition stabilized.

The lesions on the lateral thorax had healed, but the abdominal lesion persisted. On Day 365, the cat developed an approximately 5.4-cm diameter well-circumscribed SC mass on its abdomen, with sinus tracts draining purulent exudate and yellowish-white granules (Figure 3E). A clinical diagnosis of mycetoma was considered [2, 3]. On Day 372, the mass was surgically excised. Numerous fistulous tracts in the subcutaneous tissue also were resected. Histopathology indicated pyogranulomatous dermatitis composed of a mixed inflammatory infiltrate associated with dense clumps of finely granular and filamentous Gram-positive bacterial colonies, surrounded by radiating eosinophilic material, an uncommon Splendore-Hoeppli phenomenon (Figure 4A,B) [2, 3, 5].

Microbiological culture was performed using two bi-plate Petri dishes containing 5% sheep blood agar and MacConkey agar. One dish was incubated aerobically, and the other anaerobically. After 120 h, no bacterial growth was detected on the anaerobic bi-plate, ruling out actinomycosis. In contrast, the aerobic culture showed bright white, powdery colonies firmly adhered to the agar surface (Figure 4C). Microscopy showed the presence of branched filaments and characteristic Gram-positive coccobacilli (Figure 4D). Using matrix-absorption laser desorption ionization-time-of-flight mass spectrometry (MALDI-TOF MS; MALDI Biotyper CA System, Bruker Daltonics Inc), the clinical isolate was identified as *Nocardia puris*. Use of MALDI-TOF MS is a reliable method for identification of *Nocardia* isolates [2], including those of veterinary origin [3, 5].

The surgical incision healed without complications. Two months later (Day 426), the cat was clinically well, and no nodular lesions had reappeared. The nonregenerative anemia had resolved, and the cat continued to receive treatment with TMP-SFX (20 mg/kg PO q12h), clarithromycin (62.5 mg PO q24h), folic acid (1 mg/kg PO q24h), and levothyroxine (12.5 μg/kg PO q12h).

3 | Discussion

In cats, hypothyroidism is a rare condition, particularly in adults [23, 24]. The most common form is iatrogenic, occurring secondary to the treatment of hyperthyroidism with antithyroid medications, radioactive iodine, or thyroidectomy [23]. The cat described here developed hypothyroidism after prolonged treatment with potentiated sulfonamides. Sulfonamide-induced hypothyroidism in a cat has only been reported once previously [17].

In both dogs and cats, nocardiosis is associated with high morbidity and mortality [1, 3, 4, 6]. The disease is manifested in three main forms: cutaneous-subcutaneous, pulmonary, and disseminated [2, 3]. In cats, the cutaneous-subcutaneous form, as described here, is the most prevalent, accounting for approximately 75% of reported cases [1, 3]. Cutaneous-subcutaneous nocardiosis generally results from direct inoculation of the bacteria into the skin via a penetrating injury or contamination of a wound [1–3]. Although the exact source of infection could not be determined in the cat reported here, it had multiple wounds

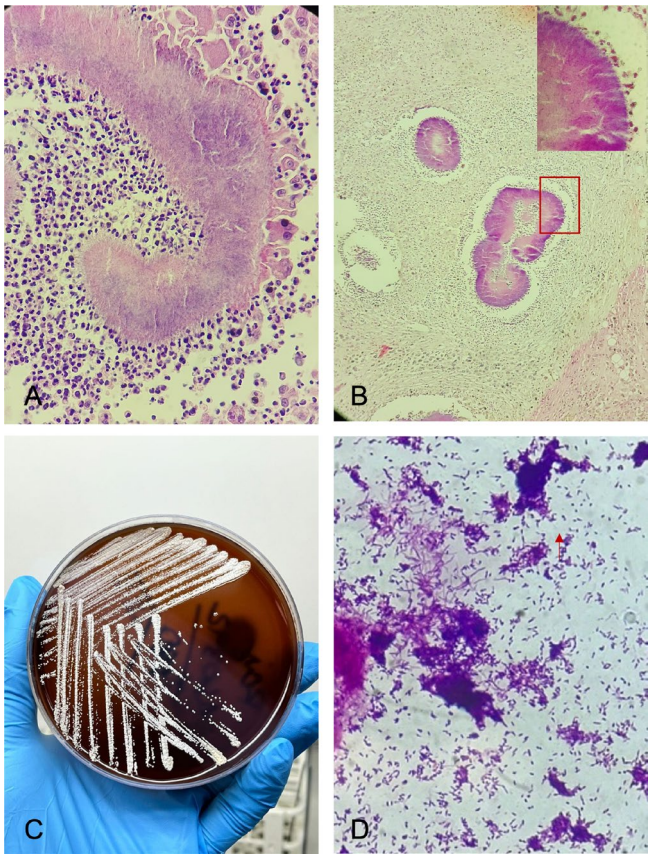

FIGURE 4 | (A) Histological section showing a mixed inflammatory infiltrate predominantly composed of neutrophils and macrophages with foamy cytoplasm, along with diffusely distributed multinucleated giant cells, and smaller quantities of lymphocytes, plasma cells and Mott cells. This region also includes dense clumps of finely granular and filamentous basophilic material (bacterial colony), surrounded by radiating eosinophilic material, a Splendore-Hoeppli phenomenon. Hematoxylin and eosin (H&E) staining, 10× objective. (B) Histological section with positive staining for finely granular and filamentous material using the Gram histochemical staining method, 10× objective (inset 100× objective). (C) *Nocardia puris* subcultured on sheep blood agar after 5 days of incubation, showing vivid white, powdery colonies that adhere firmly to the surface of the medium. (D) Microscopic view of *Nocardia puris* isolate under Gram staining (100× objective), showing branching Gram-positive filaments. Clumped structures are also visible.

at the time of rescue, suggesting that the infection may already have been present at that time.

Each *Nocardia* species has a unique pattern of antimicrobial susceptibility, but most respond well to treatment with TMP-SMX, which is the recommended empirical treatment [1–3]. Potentiated sulfonamides, such as TMP-SMX, interfere with thyroid function by reversibly inhibiting thyroperoxidase [25], an enzyme essential for the biosynthesis of thyroid hormones. This inhibition is dose-dependent and results in decreased concentrations of thyroid hormones, triggering increased thyroid-stimulating hormone (TSH) secretion from the pituitary gland because of the lack of negative feedback inhibition [23]. The sustained increase in circulating TSH causes thyroid follicular cell hyperplasia, leading to the enlargement of both thyroid lobes, a condition known as goitrous hypothyroidism [12, 14]. Our cat was diagnosed with iatrogenic goitrous hypothyroidism based on clinical history, a thyroid hormone profile, and scintigraphy findings. Both thyroid lobes were enlarged on physical examination, and thyroid scintigraphy confirmed symmetrical bilateral hyperplasia with increased radionuclide uptake. A serum thyroid profile showed low concentrations of total T4 and free T4 with a very high TSH concentration. These findings support the diagnosis of hypothyroidism caused by dyshormonogenesis [23, 24].

Our cat remained on TMP-SMX for 3 months after the initial clinical presentation and showed complete remission of skin lesions, indicating a good response to the antimicrobial treatment. However, sulfa-induced dyshormonogenesis and hypothyroidism were diagnosed during this time. As expected, the drug-induced hypothyroidism was reversed by discontinuation of TMP-SMX, as evidenced by the normalization of both T4 and TSH concentrations.

Because of the unfavorable progression and worsening of the cat's dermatologic condition, including the recurrence of deep pyoderma secondary to nocardiosis, TMP-SMX was reintroduced into the treatment regimen. Once again, rechallenge with TMP-SMX resulted in development of iatrogenic hypothyroidism. This time, progressive changes in the cat's thyroid hormone concentrations were closely monitored throughout the course of treatment. After 12 days of TMP-SMX treatment, serum TSH concentration had again increased, and T4 concentration had decreased, although both results remained within their respective RIs. However, after 30 days, serum TSH concentration had increased > 60 times its baseline concentration, and T4 was markedly decreased. Similar findings have been reported in dogs, where hypothyroidism typically develops after approximately 3 weeks of TMP-SMX administration [9, 12], a timeline comparable to that observed in our cat. The standard treatment for hypothyroidism is supplementation with synthetic levothyroxine sodium (L-T4). The recommended initial dose of L-T4 is 20–40 μg/kg/day [23]. After 36 days of treatment, serum thyroid hormone concentration had returned to normal, confirming the effectiveness of L-T4 supplementation. Ongoing monitoring of thyroid hormones is essential to guide dose adjustments, ensuring that serum T4 and TSH concentrations remain within their respective RIs [23].

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Disclosure

Authors declare no off-label use of antimicrobials.

Ethics Statement

Authors declare no Institutional Animal Care and Use Committee or other approval was needed. Authors declare human ethics approval was not needed.

Conflicts of Interest

The authors declare no conflicts of interest.

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