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CASE REPORT

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Recurrent severe neutropenia following doxycycline use in a young healthy woman

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Abstract

A 29-year-old woman was hospitalized for fever, pharyngitis, and severe neutropenia after recent use of doxycycline and other antimicrobials. Three years later, she again presented with severe neutropenia after recent doxycycline use. Diagnostic workups were unyielding. This is only the second published case of severe neutropenia associated with doxycycline use.

KEYWORDS

acute medicine, haematology, infectious diseases, pharmacology

1 | INTRODUCTION

Neutropenia is a life-threatening condition defined as a decrease in circulating neutrophils to fewer than 1500 cells/μl. The prevalence of neutropenia varies with ethnicity, age, and comorbidities, but among 25,222 subjects who participated in a cross-sectional study between 1994 to 2004, the prevalence of neutrophil counts of fewer than 1000 cells/μl was less than 1%.[1] The etiology of severe neutropenia, defined as fewer than 500 cells/μl, is varied and includes infections, drug-induced neutropenia, leukemia, lymphomas, aplastic anemia and nutritional deficiencies including vitamin B12, folate, and copper.[2] The most common antibiotic to be associated with neutropenia is trimethoprim-sulfamethoxazole, but others include cephalosporins, sulfonamides, vancomycin, dapsone, macrolides, and semisynthetic penicillins.[2] Tetracyclines are on rare occasion reported to be associated with neutropenia as part of drug-induced systemic syndromes.[3] To date, there is only one published report of neutropenia associated with doxycycline, which occurred in the setting of a very severe aplastic anemia and additionally affected other myeloid cell lines.[4] The purpose of the presented case is to highlight the need for diagnosticians to consider doxycycline as a causative agent of severe neutropenia after an extensive diagnostic workup is pursued. Our literature review highlights the relative risk of neutropenia among different antibiotics in the tetracycline class, and we determine that doxycycline is among the least likely to cause severe neutropenia.

2 | CASE HISTORY/ EXAMINATION OF INITIAL PRESENTATION

In autumn 2017, a 29-year-old woman presented to a suburban community hospital emergency department (ED) with fever after returning from a 3-week trip to Southeast Asia. Her past medical history was notable for migraines, managed with ibuprofen as required, and a prior episode of mononucleosis 17 years earlier. She was born and raised in New York City, where she worked as a marketing professional. She lived with her male partner with whom she was sexually active, monogamous, and did not use barrier

contraception. She had 2 cats at home. She had no known family history of autoimmune or hematologic disorders.

Prior to her trip, she received a hepatitis A vaccine and atovaquone-proguanil for malaria prophylaxis. During her travels to Hong Kong, Vietnam, Cambodia, and Thailand, she noted numerous mosquito bites on her lower legs but had no specific recollection of tick bites. She was symptomatically well upon returning to her home in New York, but 2 days later, she developed a swollen posterior auricular lymph node and subjective fever. She was reviewed by an otolaryngologist who prescribed a 1-week course of doxycycline. Her subjective fever improved on doxycycline; however, she developed a rash on her torso prior to finishing the course. Three days following the course, she developed an isolated fever of 38.9°C. She was otherwise well, and her rash resolved within 6 days. The following week, she had another fever of 39.4°C accompanied by severe pharyngitis and tender anterior cervical lymphadenopathy, prompting presentation to the ED.

Vital signs in the ED were temperature 38.1°C, heart rate of 86 beats per minute, blood pressure of 106/55 mm/Hg, respiratory rate of 16 breaths per minute, and oxygen saturation of 98% on room air. On physical examination, she was noted to have tonsillar enlargement with bilateral purulent exudates, an aphthous ulcer on the mucosal surface of her lower lip that was swabbed for herpes, exquisitely tender subcentimeter anterior cervical nodes, and no organomegaly. Her blood tests revealed leukopenia with a total white blood cell count of 0.9 × 1000/μl (normal range 4.0–11.0 × 1000/μl), an absolute neutrophil count (ANC) of 0.0 × 1000/μl (normal range 1.8–7.3 × 1000/μl), absolute lymphocyte count of 0.8 × 1000/μl (normal range 1.0–2.3 × 1000/μl), hemoglobin 12.2 g/dl, hematocrit 35.8%, and platelet count 201 × 1000/μl. Mean corpuscular volume (MCV) was within normal range at 87.1 fl, and red blood cell distribution width was also normal at 11.7%.

3 | INVESTIGATIONS, DIFFERENTIAL DIAGNOSIS, AND TREATMENT OF INITIAL PRESENTATION

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were both elevated at 41 mm/h and 6.1 mg/dl, respectively. Two peripherally drawn blood cultures showed no growth after 5 days, and fungal culture showed no growth after 21 days. Urinalysis and urine culture were both unremarkable, and urine pregnancy test was negative. Drug screen was not performed. She had an extensive hematologic, rheumatologic, and infectious disease workup for neutropenia, summarized in Table 1. This was largely unrevealing, aside from a positive anti-nuclear antibody (ANA) at 1:640 with homogenous pattern, but follow-up autoimmune serology was unremarkable. Rapid streptococcal testing was negative, but throat cultures grew Non-Group A, Beta-Hemolytic Streptococci after 5 days. Lactate dehydrogenase (LDH) was within normal limits at 188 U/L, and peripheral blood flow cytometry showed no evidence of hematological malignancy with the report noting mild inversion of CD4:CD8 T-cell ratio and increased circulating CD4+ CD16/56+ NK cells, as can be seen in reactive processes. Human Immunodeficiency Virus (HIV) 1/2 testing via antigen/antibody as well as via PCR were all negative. The patient was very mildly anemic based on hematocrit, and anemia work-up found normal folate of 10.6 ng/ml, elevated ferritin of 380 ng/ml, low vitamin B12 at 219 pg/ml (normal range 254–1320 pg/ml), and positive intrinsic factor antibody (gastric parietal cell antibody negative). Thyroid stimulating hormone was within normal limits. She declined bone marrow biopsy but agreed to undergo a biopsy if there was no improvement of her neutrophil count within days.

Due to her combination of neutropenia, recent travel and acute symptoms of pharyngitis and rash, bacterial and viral infections topped the list of differentials. Despite extensive testing, the results were unyielding aside from a positive throat culture. Leukemia and lymphoma were considered but unlikely given the LDH was within normal limits and flow cytometry was negative. Due to concomitant presentation of mild anemia, vitamin B12 and folate levels were tested and found to be slightly low and within normal limits, respectively. The hematologist felt it was unlikely that mild vitamin B12 deficiency could cause severe neutropenia in setting of normal hemoglobin, normal MCV, and only slightly decreased hematocrit. Autoimmune workup was largely unrevealing. Hemophagocytic lymphohistiocytosis (HLH) was considered but deemed unlikely due to the normal platelet count and ferritin level that was only 380 ng/ml. Drug-induced neutropenia was also considered as the patient had recently completed courses of atovaquone-proguanil and doxycycline, but the patient had no bloodwork between her return from her trip to Asia and her presentation to the ED to establish a clear timeline of events. Oropharyngeal tularemia was consistent with the patient's initial presenting symptoms and signs but was not investigated for because of her positive throat culture for Non-Group A, Beta-Hemolytic Streptococci.

Antimicrobial therapy with piperacillin-tazobactam, acyclovir, and fluconazole were initiated, and she was started on filgrastim. She was given a total of two 1,000 mcg injections of cyanocobalamin. By Day 5, her neutrophil counts had improved to 1.0 × 1000/μl, rendering further bone marrow testing unnecessary, and filgrastim was discontinued. Negative HSV testing resulted in

TABLE 1 Laboratory studies conducted to investigate the cause of neutropenia

Study	Normal range	2017 workup	2020 workup
Hematology			
Granulocyte Ab, Granulocyte agglutination assay	Negative	Negative	–
Granulocyte immunofluorescence assay (GIF flow cytometry)	Negative	Negative	–
Flow cytometry	Negative for malignancy	Negative for malignancy	Negative for malignancy
Vitamin B12	211–911 pg/ml	219	649
Folate	>5.4 ng/ml	10.6	18.8
Rheumatology			
Rheumatoid factor	0–14 IU/ml	–	<10.0
ANA	Negative	Positive	Positive
ANA titer and pattern	<1:160, none	1:640, homogenous	1:1280, homogenous
Centromere Ab	0.0–0.9 AI	<0.2	<0.2
Smith Ab	0.0–0.9 AI	<0.2	<0.2
SS-A Sjogrens Ab	0.0–0.9 AI	0.2	<0.2
DsDNA Ab	0.0–4.0 IU/L	<1.0	1.0
SS-B Sjogrens	0.0–0.9 AI	<0.2	<0.2
Scl-70	0.0–0.9 AI	<0.2	<0.2
Jo-1 IgG Ab	0.0–0.9 AI	<0.2	<0.2
Anti-Ribosomal p	0.0–0.9 AI	<0.2	<0.2
Anti SM/RNP	0.0–0.9 AI	<0.2	<0.2
RNP Ab	0.0–0.9 AI	0.3	0.7
Chromatin (histone)	0.0–0.9 AI	<0.2	<0.2
Proteinase 3 IgG Ab	0.0–0.9 AI	<0.2	–
GBM Ab	0.0–0.9 AI	<0.2	–
Myeloperoxidase Ab	0.0–0.9 AI	<0.2	–
Vector disease			
Lyme IgG and IgM	Negative	Negative	Negative
Babesia smear	Negative	Negative	–
Malaria smear	None seen	None seen	–
Anaplasma phagocytophilum DNA PCR	Not detected	–	Not detected
Virology			
SARS COV-2 (COVID-19) RNA	Negative	–	Negative
Adenovirus	Not detected	Not detected	Not detected
Dengue fever virus IgG and IgM	<0.80	<0.80	–
Parainfluenza virus 1,2,3,4	Not detected	Not detected	Not detected
Rhinovirus	Not detected	Not detected	Not detected
Influenza A, A H1, A H3	Not detected	Not detected	Not detected
Influenza B	Not detected	Not detected	Not detected
Human Metapneumovirus	Not detected	Not detected	Not detected
RSV A	Not detected	Not detected	Not detected
RSV B	Not detected	Not detected	Not detected
CMV IgG, IgM	Not detected	Not detected	–

(Continues)

TABLE 1 (Continued)

Study	Normal range	2017 workup	2020 workup
CMV quantitative PCR	Not detected	Not detected	–
EBV heterophile Ab (monospot)	Negative	Negative	Negative
A. Phagocytophilum DNA	Negative	–	Negative
HSV-1/HSV-2 PCR	Negative	Negative	–
HSV-1/HSV-2 IgG, IgM	Negative	Negative	–
HIV ½ screen	Negative	Negative	–
HIV PCR log copies/ml	<1.30 cps/ml	<1.30	–

discontinuation of acyclovir. Antibiotics were changed to oral amoxicillin-clavulanic acid after throat culture results were available.

4 | OUTCOME AND FOLLOW-UP OF INITIAL PRESENTATION

The etiology was believed to be a viral syndrome causing neutropenia or a drug-induced neutropenia with superimposed bacterial pharyngitis, but due to multiple recent courses of antimicrobials, it was unclear which medication would have been the true culprit. The patient was discharged home with instructions to complete a course of amoxicillin-clavulanate and receive vitamin B12 supplementation. She had outpatient bloodwork performed 1 month post-discharge that was notable for absence of Lyme IgG and IgM antibodies, normal white blood cell count, normal hemoglobin/hematocrit, normal platelet count, and ANC 3.66 × 1000/μl. She saw her primary care provider 2 years after discharge for an annual physical examination and reported that she had stopped taking vitamin B12 for the prior year. However, laboratories at this time showed normal vitamin B12 of 552 pg/ml and normal folate of 18.3 ng/ml. Her white blood cell count of 4.84 × 1000/μl, absolute neutrophil count 2.09 × 1000/μl, hemoglobin 13.0 g/dl, hematocrit of 37.9%, and MCV 88.6 fL were all within normal limits. Sexually-transmitted infection testing including HIV, syphilis, hepatitis B, hepatitis C, gonorrhea, and chlamydia were all negative.

5 | HISTORY/EXAMINATION OF RECURRENCE

She re-presented to the ED in August of 2020 with fever, arthralgias, and painful lymphadenopathy. On this occasion, she had been seen by a dermatologist 3 weeks prior for recurrent perioral and periorbital dermatitis and started on a doxycycline course. The day following commencement of doxycycline, she had developed fever and arthralgias involving her hands. She had continued to take doxycycline as prescribed for 6 days until her dermatologist recommended that she discontinue. However, the patient continued to feel unwell during this time, and 10 days after her final dose of doxycycline, she developed tender cervical adenopathy and low-grade fever up to 37.8°C which continued for several days, prompting this visit to the ED.

Her vitals were heart rate 79 beats per minute, blood pressure 116/56 mm/Hg, respiratory rate of 18 breaths per minute, oxygen saturation of 98% on room air, and her temperature ranged from 37.2°C to 38.9°C. Physical examination revealed a well-nourished, well-appearing woman with mild tonsillar swelling, right greater than left, mildly tender bilateral cervical chain 1 cm lymph nodes, faint right periorbital dermatitis, and no organomegaly. Her complete blood count with differential revealed white cell count of 2.9 × 1000/μl, neutrophil count of 0.0 × 1000/μl, and lymphocyte count of 2.3 × 1000/μl.

6 | INVESTIGATIONS, DIFFERENTIAL DIAGNOSIS, AND TREATMENT OF RECURRENCE

Her blood smear was significant for leukopenia, neutropenia, and relative lymphocytosis with abnormal appearing lymphocytes. Laboratories were further remarkable for an ESR of 39 mm/h, CRP of 3.4 mg/dl and ANA positive to 1:1280, but follow-up rheumatologic serology was again negative. A similar workup to her 2017 admission was undertaken and is summarized in Table 1. Vitamin B12 this time was normal at 649 pg/ml. Pregnancy test was again negative, and both LDH and TSH were within normal limits. Respiratory virus panel and SARS-CoV-2 RNA testing via nasal swab were negative. Drug screen was not performed. Repeat peripheral blood flow cytometry yielded similar results as before with inverted CD4:CD8 ratio with increased, atypical immunophenotype T-large granular lymphocytes, representing about 21–22% of total cellularity, which may be consistent with a reactive process.

The differential diagnoses for this second presentation of febrile neutropenia in the setting of recent doxycycline exposure were similar to her previous admission in 2017 when there was a high suspicion of drug-induced neutropenia. At that time, there were several confounding variables which, combined with a myriad of mixed tests results, weakened the resolve to label the syndrome as a drug-induced reaction. On revealing this suspicion that doxycycline may be to blame, the patient relayed she had similarly experienced arthralgia after a course of minocycline for acne as a teenager. She did not recall fever at that time, nor did she undergo any workup because the symptoms resolved after completion of the minocycline course. Cyclic neutropenia was considered but deemed less likely because of the relative rarity of these episodes.

She was started on piperacillin-tazobactam and filgrastim for neutropenic fever. On Day 2 of her admission, ANC improved to 2.9 × 1000/μl, and she remained afebrile and reported only a mild headache. Piperacillin-tazobactam and filgrastim were discontinued upon discharge on Day 3.

7 | OUTCOME AND FOLLOW-UP OF RECURRENCE

Repeat complete blood count 4 days after discharge showed ANC of 6.2 × 1000/μl. She was advised to avoid the use of any tetracyclines and was followed by rheumatology and hematology specialists as an outpatient. She has had no further flares of neutropenia to date, making cyclic neutropenia even less likely.

8 | DISCUSSION

The commonly encountered adverse effects of doxycycline include photosensitivity, esophageal erosion, and other gastrointestinal symptoms.[3,5,6] Rarely reported side effects include Stevens–Johnson Syndrome, hypoglycemia, drug-induced fever, and amnesia.[7–10] A diagnosis of doxycycline-induced neutropenia in our case is favored by the recurrence of neutropenia with repeat doxycycline exposure and remission with cessation, bolstered by granulocyte colony-stimulating factor administration. This is further supported by the extensive and conclusively negative diagnostic workup (summarized in Table 1). We believe this is the first reported case of doxycycline-induced neutropenia that has not affected other myeloid cell lines. As aforementioned, a rigorous literature search found only one published report of neutropenia associated with doxycycline that occurred in the setting of a very severe aplastic anemia.[4] In our case, it is unclear if without treatment with filgrastim or timely cessation of the antibiotic, there would have been a progression to suppress other myeloid cell lines. There is no published evidence that reflects doxycycline's ability to cause other hematopathology other than eosinophilia associated with drug-induced hypersensitivity syndrome.[11]

Among the Tetracycline class of antibiotics, we found prior case reports of minocycline causing neutropenia as part of drug-induced systemic syndromes including drug-induced autoimmune hepatitis, drug-induced lupus, and a syndrome of fever, eosinophilia, and lymphadenopathy which is also known as DRESS (drug reaction with eosinophilia and systemic symptoms) Syndrome.[12-14] Tigecycline has also been reported to cause neutrophil engraftment delay in two pediatric patients following bone marrow transplant with infectious complications.[15] A comparative safety review of tetracycline, doxycycline, and minocycline in 1997 did not report any cases of neutropenia induced by doxycycline.[3] For this reason, we still consider doxycycline to be a medication that is very unlikely to cause neutropenia despite our experience with this case.

Our case illustrates that an extensive differential diagnosis must be considered to ascribe a novel adverse effect to a medication. As part of our patient's first presentation of illness, her throat culture grew Non-Group A, Beta-Hemolytic Streptococci. Non-Group A strep is a known cause of bacterial pharyngitis. A 3-group retrospective case-control study with sample size of 915 and mean age of 26 years old found that among young adults with acute pharyngitis, non-Group A Strep infection was as common as Group A Strep (GAS) infection and was associated with the same clinical features typically associated with GAS.[16] Therefore, while other conditions such as oropharyngeal tularemia and Kikuchi–Fujimoto disease (KFD) were not specifically investigated, the likeliest trigger for each episode of severe neutropenia was doxycycline. KFD presents with neutropenia, atypical lymphocytes, and cervical lymphadenopathy, all of which are consistent with our patient's initial presentation. However, this was not deemed the likeliest diagnosis given the rarity of KFD outside of East Asia, the time course of her recurrent neutropenia consistently being preceded by doxycycline, and her clinical improvement with cessation of doxycycline and administration of filgrastim rather than the use of any corticosteroids.[17]

The patient's arthralgia in the setting of a strongly positive ANA may have suggested a drug-induced lupus with neutropenia. However, this appears less likely given the short length of exposure to the drug and that the remainder of the autoimmune panel was negative. While

there are no standardized diagnostic criteria for drug-induced lupus, it is generally accepted that there has been drug treatment for at least 1 month prior to the development of symptoms.[18,19] It is also usually associated with positivity of other autoimmune antibodies beyond ANA, especially anti-histone antibodies.[18,19] Potential pathophysiologic mechanisms for doxycycline-induced neutropenia include autoimmune-mediated destruction of mature granulocyte precursor cells or decreased granulopoiesis, as postulated for minocycline in a prior case report.[13] An autoimmune-mediated etiology would appear more likely in our case, given the strongly positive ANA. We theorize that childhood exposure to minocycline may have caused the initial priming immune response that was further potentiated by her later exposures to doxycycline. Further studies would be required to elucidate the exact pathophysiologic mechanism.

In conclusion, this case and our review illustrates that neutropenia is an extremely rare but serious side effect of doxycycline that should be considered in the differential diagnoses of febrile neutropenia. It would be prudent to list neutropenia as a rare but serious side effect of doxycycline and given that cross reactivity among the class of antibiotics is as yet unknown, we would consider avoidance of tetracyclines following an episode of doxycycline-induced neutropenia. This patient was labeled as allergic to tetracyclines moving forward, and she was educated about this side effect. Despite our experience with this patient, if a tetracycline antibiotic is indicated for use in a different patient in whom neutropenia is a serious concern, we would still favor doxycycline as among the safest to use.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

Michael Foti as first author (MF) reviewed all cited literature, wrote initial draft of discussion section, and made revisions to all sections for clarity, accuracy, and inclusion of additional intellectual content. Tushaar V. Shrimanker as second author (TVS) reviewed cited literature, wrote initial drafts of clinical summary sections, revised initial drafts of all sections, acquired relevant clinical data, and created table. Umar N. Hasan as third author (UNH) reviewed cited literature, wrote initial draft of introduction section, revised drafts of all sections for clarity, accuracy, and inclusion of additional intellectual content. Khalil I. Hussein as final author (KIH) was responsible for the initial design of this work, reviewed all cited literature, acquired relevant clinical data, and revised drafts of all sections for important intellectual content.

ETHICAL APPROVAL

Our institutional review board (IRB) does not require that case reports be submitted for IRB approval.

CONSENT

The subject of this case report gave written consent to submit this case report for publication.

DATA AVAILABILITY STATEMENT

Data are not available due to privacy/ethical restrictions.

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