Differential Diagnosis of Fever of Unknown Origin in Drug Reaction with Eosinophilia and Systemic Symptom (DRESS)

Kevin Fachri Muhammad, Ferdy Ferdian, Andri Reza Rahmadi

Department of Internal Medicine, Faculty of Medicine Universitas Padjadjaran
Dr. Hasan Sadikin General Hospital Bandung, Indonesia

pISSN: 2302-1381;
eISSN: 2338-4506;
http://doi.org/10.15850/ijihs.v10n1.2198
IJIHS. 2022;10(1):39-45

Received:
November 8, 2020

Accepted:
March 23, 2022

Abstract

Objective: To describe an unusual case of drug reaction with eosinophilia and systemic symptoms presenting as fever of unknown origin (FUO) and the diagnostic hurdles that come with the presence of differential diagnosis of FUO, which is tuberculous lymphadenitis.

Methods: A 34-year-old female with a chief complaint of fever that has lasted for 3 weeks accompanied with jaundice and skin rashes for 2 weeks was admitted with an indication of FUO. She had a history of carbamazepine consumption for trigerminal neuralgia 2 months prior. Cervical lymphadenopathy was palpable bilaterally and hepatomegaly, elevated liver enzyme, as well as hyperbilirubinemia were observed. After excluding differentials for many causes of prolonged fever, patient was treated for Drug Reaction with Eosinophilia and Systemic Symptom (DRESS) and was given intravenous steroid injections. Fine needle aspiration biopsy was performed for her cervical lymphadenopathy.

Results: Biopsy presented a mix of sialadenitis and tuberculous lymphadenopathy. Clinical improvement was observed on the second day after steroid administration. Patient was discharged on the seventh day after steroid administration.

Conclusion: FUO is one of the possible manifestations of DRESS; however, thorough investigation still needed to be done considering the possibility of more than one entity of disease that can cause FUO in patients, such as tuberculous lymphadenopathy seen in this case.

Keywords: Case report, DRESS, drug reaction, fever of unknown origin, treatment

Introduction

In some cases, fever can continue indefinitely, thus called as a fever of unknown origin (FUO). Before etiologic cause is decided, administration of empiric therapy is not recommended although in selected cases administration of corticosteroid and broad-spectrum antibiotics is allowed. In drug reaction with eosinophilia and systemic symptom (DRESS), fever is one of the possible symptoms that can manifest. Reports on FUO related to DRESS is scarce. Here, this study present a case of FUO as a manifestation of DRESS in the presence of tuberculous lymphadenopathy which discovered much later. This study will unfold its clinical picture, disease history, workup, and treatment.

Cases

A 34-year-old came female with a chief complaint of fever that lasted for 3 weeks before admission to the hospital. The patient experienced continuous fever, higher in the evening, gets better after consuming antipyretic but return after a few hours. There is no apparent symptom of infection such as

Correspondence:
Kevin Fachri Muhammad,
Department of Internal Medicine, Faculty of Medicine Universitas Padjadjaran-Dr. Hasan Sadikin General Hospital Bandung, Indonesia
Email: kevinfachri@gmail.com

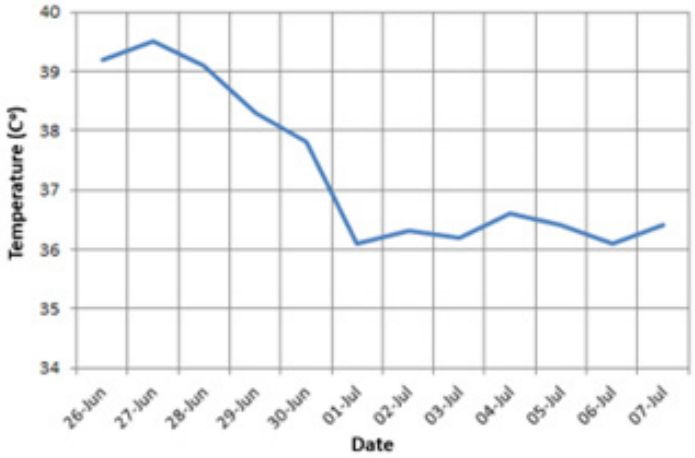

Fig. 1 Temperature Curve

cough, runny nose, dyspnea, earache, and dysuria. This complaint was accompanied by nausea, vomiting, and stomachache. Patient had a history of drug consumption in the last 2 months, for her trigerminal neuralgia that was diagnosed by her neurologist and was treated with carbamazepine tablet 2x500 mg a day. There is no history of close contact with tuberculosis patient nor history of tuberculosis medication. There is no history of prolonged cough, night sweat, although there is a loss of 2 kilograms of bodyweight for 1 month. Patient was married and have 2 children, there's no history of miscarriage, hair loss, previous skin rash or photosensitivity. Four days after the onset of her fever, she seeks treatment to a private hospital, and was told that her skin condition was caused by carbamazepine. However, after 2 weeks of hospital stay, her fever persists, and she was referred to the hospital.

The patient was compos mentis and axilla measured temperature was 39°C. She was icteric, having multiple non-tender cervical lymph node enlargement, hepatomegaly, generalized confluent skin lesion with irregular border consisted of erythematous macule and desquamation that cover her entire skin.

On laboratory examination this study found increased liver aspartate transferase (AST) 248 U/L, alanine transferase (ALT) 492 U/L, total bilirubin 5.739 mg/dL, conjugated bilirubin 5.040 mg/dL, unconjugated bilirubin 0.699 mg/dL, with negative anti-HCV, anti-HIV, and HbsAg. On blood smear microscopy, this study found atypical lymphocyte. Two ziehl-neelsen-stained sputum samples result was negative. Chest x-ray interpretation was bilateral bronchopneumonia. Abdominal ultrasound from previous hospital revealed

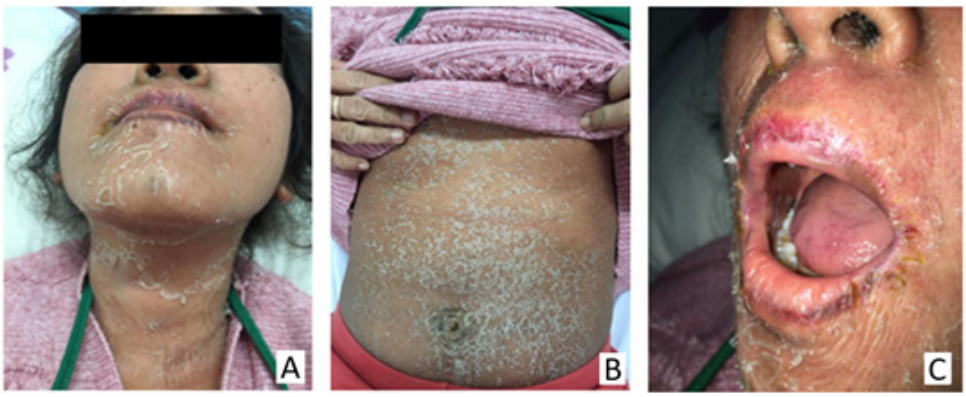

Fig. 2 (A, B) Skin Desquamation; (C) Oral Thrush with Exfoliative Cheilitis

inhomogeneous liver parenchyma with resembling starry sky that suggests inflammatory process.

She was given paracetamol 3x500 mg per oral, fluconazole 1x150 mg per oral, omeprazole 1x40 mg intravenous, curcuma 3x1 tablets per oral. From dermatology consult, this patient was suspected as having drug reaction with eosinophilia and systemic symptom (DRESS). Patient was given dexamethasone 7,5 mg intravenous per day, cetirizine 10mg per day, Vaseline for her skin.

Since steroid administration, liver function was measured regularly, and it was found that transaminase level improved along with her skin rash and jaundice. Repeat blood smear examination was done and the atypical lymphocyte was not found. All her initial symptom has already diminished, from skin rashes, lymphadenopathy, liver enlargement, and jaundice. Patients were discharged on the 13th day. Her biopsy result came out at the same day, revealing necrotic mass with fibrin, lymphocyte, epithelioid cell, and Langhans giant cell for her right cervical lymph. For her left cervical lymph shows necrotic mass, lymphocyte, polymorphonuclear cell, columnar cell, epithelioid, without Langhans giant cell. Pathology expertise concludes that her right cervical lymph was tuberculous lymphadenitis, and her left was sialadenitis. Because of that result, we give her referral for tuberculosis clinic visit after she was discharged for further treatment and evaluation.

Discussion

Fever of Unknown Origin (FUO) is an increased body temperature (higher than 38,2oC) for three weeks or more without clear etiology even after extensive evaluation for at least 1-week in hospital. There's no official guideline nor there is standardized approach to diagnose this condition.[1] According to Durack and Street, FUO can be classified into 4 type: 1) Classical FUO, fever longer than 3 weeks with unidentified cause after 3 days in hospital evaluation or more than 3 times outpatient visits, 2) Nosocomial FUO, fever that manifested after 48 hours in hospital care without clear diagnosis after 3 days in hospital evaluation, 3) Neutropenic FUO, fever with neutrophil count less than 500 cell/uL without clear diagnosis after 3 days in hospital evaluation, 4) HIV-related FUO, fever afflicting known HIV patient that was diagnosed more than 4 weeks in an outpatient setting, or diagnosed as HIV in hospital for more than 3 days.[2] The patient experience fever for 24 days before admitted in hospital, with previous 16 days inpatient care in another hospital, thus fulfilled classical FUO criteria.

There are more than 200 diseases that may became FUO differential diagnosis, subgroup of differentials that usually used in classical FUO consist of 4 categories: infection, malignancy, rheumatoid diseases, and other causes.[1] Each subgroup have distinct clinical characteristic. Malignant etiology tends to cause early anorexia and significant weight loss, while infectious etiology may cause chill without apparent weight reduction. Vasculitis and synovitis are signature clue for rheumatic etiology.3 Drug related fever can be found in 1-3% of FUO cases.[1]

Most experts suggested a wide array of standard testing panel, including blood tests, urinalysis, fecal examination, skin tests, and culture from different specimen, chest x-ray, and abdominal ultrasound. If there's still no definite diagnosis, Mourad states that its acceptable to order other tests such as hepatitis testing, liver biopsy, culture for mycobacteria, fungi, and other bacteria, echocardiography, abdominal and chest CT scan, and temporal artery biopsy for patient older than 55 years.[4] The patient disease history began when she complained of severe headache that was treated with carbamazepine, followed by appearance of fever and skin rashes. She does not have history of staying on an endemic area nor surgery. She previously had a history of hospital stay, though she did not have her medication history on that hospital with her. She already did several of the examination suggested above, which is blood exam, ziehl neelsen stain for sputum sample, chest x-ray, abdominal ultrasound. From this data, differentials were made, and rheumatologic condition was excluded from etiological possibility. Infection and malignancy were still possible at the time, considering her fever, weight loss, lymph enlargement that has yet to be examined histopathologically. From her initial blood exam, she has known to have anemia, increased conjugated bilirubin, and transaminase. Abdominal ultrasound revealed liver inflammation, previously suspected as drug induced liver injury, though after dermatology consultation, concluded that it may be related to the possibility of DRESS involvement.

Drug reaction with eosinophilia and systemic symptom (DRESS) is an adverse drug reaction (ADR) that may potentially

life threatening. This disease has multiorgan manifestation, including hematologic, hepatic, renal, pulmonary, cardiac, neurologic, gastrointestinal, and endocrine system. Dermatological manifestation in DRESS can be diverse, with morbilliform rash as its common sign. This syndrome have 10% mortality rate, usually derived from fulminant hepatitis with hepatic necrosis.[5]

A systematic review from PubMed-MEDLINE, January 1997 to May 2009 stated that there are 44 drugs that was associated with 172 reported cases. Carbamazepine was the most frequently reported drug and was found in 47 cases (27% from total cases in this series).[6]

DRESS syndrome can manifest 2 months after drug consumption, although its usually happened 2–6 weeks after the patient first exposure to drug. Symptom may appear earlier and heavier to those with repeated exposure to offending drug. Carbamazepine had an onset of 21–28 days.[7] The patient clearly said her medication history with carbamazepine 2 months before, and she became feverish 5 weeks after that.

Usual clinical manifestation for DRESS patient are fever, rash, lymphadenopathy, leukocytosis, and liver function abnormalities. Skin afflictions are explicitly clear, urticaria and maculopapular rash being the most common, though vesicle, bullae, pustule, cheilitis, purpura, target lesion, and erythroderma were also reported.7 Although skin eruption in DRESS is extensive, its morbidity and mortality were caused by systemic involvement. The most common involvement was fever (temperature >38°C) in 95% of cases with visceral organ involvement from lymphatic, hematology, hepatic, followed by renal, pulmonary, and cardiac. Severe and atypical cases can involve neurology, gastrointestinal, or endocrine dysfunction. Certain drugs may have specific organ predilection.[5] The patient was afflicted with extensive skin lesion in the form of erythematous macule and desquamation.

Lymphadenopathy, local or generalized, can be found on 75% of DRESS. The most common lymph node involvement was in cervical, axillary, and inguinal area. Histopathologically, there's 2 main variant, benign and pseudo-lymphomatous type.[8]

Hematological disturbance was frequently encountered and happened 2 weeks after drug eruption onset. Leukocytosis, with high atypical lymphocyte that preceded by leukopenia or lymphopenia, with eosinophilia that may contribute to visceral organ manifestation. There is also thrombocytopenia and anemia.[8]

Hepatic involvement may manifest as hepatocellular or cholestatic liver injury, and on severe cases may become fulminant hepatic failure that require liver transplantation.8 DRESS could be included in one of the phenotypes of drug-induced liver injury (DILI), and some authors recommend the DILI severity index to evaluate the degree of liver injury. It is described that patients with severe acute liver damage may shows an overall survival of 75%, with hepatic encephalopathy, factor V level, prothrombin time were predictors of poor prognosis.[9]

Lung involvement from DRESS may decrease lung capacity as this condition may take form as acute interstitial pneumonitis, lymphocytic interstitial pneumonia, pleuritis, and acute respiratory distress syndrome (ARDS). Lung involvement may also be described by signs such as cough, dyspnea, pleuritic pain and/or radiological findings such as unilateral or bilateral pulmonary infiltrates, lobar infiltrates, and pulmonary nodules.[10]

The patient had many symptoms that formerly thought as several diseases, eventually all those symptoms can be explained as systemic manifestation of DRESS. She had bilateral cervical lymphadenopathy, hematological manifestation in the form of anemia and atypical lymphocyte. She got cholestatic type liver injury with jaundiced sclerae, hepatomegaly that was confirmed by physical exam and ultrasound, increased AST/ALT and conjugated bilirubin. There is no increase in BUN nor creatinine, but we found microscopic hematuria. Lung involvement can be suspected from bilateral infiltrate on her chest x-ray, that was interpreted as bronchopneumonia, in the absence of symptom and sign of infection.

Patient suspected with DRESS must undergo extensive evaluation. Deciding the associated drug oftentimes difficult in polypharmacy or when symptom appeared after long latency period. Clinical examination that was developed to point out DRESS causative agent was not reliable. Regular testing method that was used is skin patch test and lymphocyte transformation test (LTT). Systematic review show that PPV from skin patch test in optimal setting can be as high as 80–100%. For optimal result, patch test must be done 2–6 months after resolution of symptom. Positive LTT result consequential in

diagnosis and determining causative drug in DRESS. Negative LTT result could not rule out drug hypersensitivity.[11] The patient' causative drug can be easily identified so further examination was not required.

Up until this point there's no gold standard diagnostics for DRESS. European Registry of Severe Cutaneous Adverse Reaction Study Group invent scoring system called RegiSCAR, based on the criteria invented by Bocquet et al. Japanese consensus group also used the same criteria with different terminology, which they called Drug Induced Hypersensitivity Syndrome (DIHS).[7] This study was calculated RegiSCAR score on the patient with a total score of four, interpreted as probable DRESS.

Common differential for DRESS is other systemic cutaneous adverse reaction (SCAR), such as Stevens Johnson syndrome/toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and erythroderma which also manifesting skin lesion and visceral involvement. It is important to differentiate DRESS from dermatological findings from exanthem virus (Kawasaki, EBV, viral hepatitis, influenza, CMV, and HIV). DRESS also have to be differentiated from lymphoma, pseudo-lymphoma, collagen vascular disease, serum sickness-like reaction. Other differentials include Kawasaki syndrome, Still's Disease, syphilis, porphyria, and hypereosinophilic syndrome.[12]

In the beginning, this study did not administer any treatment for the patient. The reason was because empirical therapy was not recommended in patient with FUO, as it may cloud disease manifestation and delay diagnosis, thus may hindering proper treatment.[4]

Patient without clear diagnosis and clinical improvement advised to be kept on as minimal medication as possible and wait. Antipyretic can mask patient symptom and can only be given to those who were unable to tolerate their fever. In a certain working diagnosis, empiric therapy is allowed, for example empiric antibiotic is given in bacterial endocarditis even though its blood culture turn out to be negative, antituberculosis drug is given in suspected tuberculosis infection, and glucocorticoid is administered in suspected temporal arteritis with risk of blindness.4 Consultation with subspecialists (infectious disease specialist, rheumatologist, haemato-oncologist) is the correct way to get an insight on working diagnosis.[1]

The biggest challenge in DRESS is early identification of this condition and termination of causative drug. Inability to do so may increase morbidity and mortality.11 All patients must be given adequate supportive measures to stabilize their hemodynamics, given antipyretic for their fever, emolien and topical steroid for their skin condition. Empirical antibiotic must be avoided because it can cross-react with other drugs and may exacerbate the condition.[7] Systemic corticosteroid is the main therapeutic option for DRESS. It was given in prednisone equivalent dose of 1mg/kg/day. Steroid must be tapered slowly in 6-8 weeks, even after clinical resolution is achieved, to prevent relapse. It was done in this fashion because DRESS patient also has higher risk to experience immune reconstitution inflammatory syndrome if steroid is withdrawn recklessly.[7,13] Severe cases or where DRESS is refractory to conventional steroid dose, intravenous methylprednisolone can be given in pulse dose of 30mg/kg/day for 3 days.11 Intravenous immunoglobulin (IVIG) have been tried before in patient unresponsive to steroid or had contraindication to steroid.[14]

Other modalities in DRESS treatment are plasmapheresis and immunosuppressive drug such as cyclophosphamide or cyclosporine. N-acetylcysteine may help to detoxify circulating drug and limit reactive metabolite in anticonvulsant induced DRESS. Valgancyclovir can minimize complication related to HHV-6 reactivation and can be given in combination with prednisone.[15] The patient is given steroid therapy as described, using dexamethasone 7.5 mg intravenously per day (equivalent to 50mg prednisone, based on the patient body weight). Her skin affliction gradually gets better, along with her other systemic symptoms. This study repeat her blood smear, and the atypical lymphocyte is nowhere to be found. Interestingly, her leukocyte and thrombocyte increased significantly on the 5th day since steroid administration (24110/uL and 959,000/uL respectively). This may be caused by high dose steroid effect, because the patient was getting better and there is no sign of infection. Patient who received 40–80 mg prednisone-equivalent may have leukocytosis since a few hours to 2 weeks after administration.[16] Corticosteroid was also known to cause transient thrombocytosis through splenic release of pooled thrombocyte into systemic circulation.[17]

Histopathologically, drug induced lymphadenopathy is flooded with polymorphic cellular infiltrate comprised of lymphocyte, plasma cell, eosinophil, and histiocyte. Some may have focal hemorrhagic necrosis without

fibrosis, with endothelial hyperplasia. On the other hand, tuberculous lymphadenopathy showed epithelioid granuloma with giant Langhans cell accompanied with central necrosis.[18] The patient showed tuberculous characteristic on her right lymph node biopsy, though on her left lymph node it was found to support drug reaction because histopathologically comprised more with lymphocyte and polymorphonuclear cell. Another reason why tuberculosis cannot be excluded completely is that steroid was used. Anti-inflammatory effect from corticosteroid may null the body fever generating mechanism through prostaglandin inhibition from arachidonic acid release blockade. Corticosteroid also able to halt interleukin-1 transcription which is important to augment T-cell proliferation.[19] However, we know that DRESS's mortality and morbidity is caused by its systemic involvement. Fever is manifested in 90% cases and usually very high in DRESS (>38°C), while in tuberculous lymphadenitis, systemic manifestation is uncommon, and fever is reported in HIV coinfection as a low-grade fever. In immunocompetent patient, fever only reported in 20–50% cases.[7]

Therefore, this study conclude from the patient characteristics, that DRESS is the main cause of fever in this patient. Diagnosis of DRESS must be suspected from the symptom of skin rash, liver involvement, fever, and lymphadenopathy in patient with history of drug use. FUO is one of the possible manifestations of DRESS, but thorough investigation still needed to be done, considering the possibility of more than one entity of disease that can cause FUO in one patient. Termination of drug, accurate treatment, supportive measures, wound care, multidisciplinary approach, and early systemic steroid initiation is crucial to reduce mortality and morbidity in DRESS.

References

1. Hersch EC, Oh RC. Prolonged febrile illness and fever of unknown origin in adults. Am Fam Physician. 2014;90(2):91–6.
2. Varghese GM, Trowbridge P, Doherty T. Investigating and managing pyrexia of unknown origin in adults. BMJ. 2010;341:878–81.
3. Cunha BA, Lortholary O, Cunha CB. Fever of unknown origin: a clinical approach. The Am J Med. 2015;128:1138.e1-1138.e15.
4. Unger M, Karanikas G, Kerschbaumer A, Winkler S, Aletaha D. Fever of unknown origin (FUO) revised. Wien Klin Wochenschr. 2016;128(21-22):796–801.
5. Husain Z, Reddy BY, Schwartz RA. DRESS syndrome: part I. clinical perspectives. J Am Acad Dermatol. 2013;68:693.e1–14.
6. Mardivirin L, Valeyrie-Allanore L, Branlant-Redon E, Beneton N, Jidar K, Barbaud A, et al. Amoxicillin-induced flare in patients with DRESS (drug reaction with eosinophilia and systemic symptoms): report of seven cases and demonstration of a direct effect of amoxicillin on human herpesvirus 6 replication in vitro. Eur J Dermatol. 2010;20:68–73.
7. De A, Rajagopalan M, Sarda A, Das S, Biswas P. Drug reaction with eosinophilia and systemic symptoms: an update and review of recent literature. Indian J Dermatol. 2018;63(1):30–40.
8. Kano Y, Ishida T, Hirahara K, Shiohara T. Visceral involvements and long-term sequelae in drug-induced hypersensitivity syndrome. Med Clin North Am. 2010;94:743–59.
9. Delgado MG, Casu S, Montani M, Brunner F, Semmo N, Berzigotti A, et al. Hepatic manifestations of drug reaction with eosinophilia and systemic symptoms syndrome. Exploration Med. 2021;2:122–34.
10. Taweesedt PT, Nordstrom CW, Stoeckel J, Dumic I. Pulmonary manifestations of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: a systematic review. Biomed Res Int. 2019;2019:7863815.
11. Husain Z, Reddy BY, Schwartz RA. DRESS syndrome: Part II. Management and therapeutics. J Am Acad Dermatol. 2013;68:709.e1–9.
12. Kumari R, Timshina DK, Thappa DM. Drug hypersensitivity syndrome. Indian J Dermatol Venereol Leprol. 2011;77:7–15.
13. Shiohara T, Kano Y. Review of drug-induced hypersensitivity: Special emphasis on drug-induced hypersensitivity syndrome. Expert Rev Dermatol. 2012;7:539–47.
14. Kito Y, Ito T, Tokura Y, Hashizume H. High-dose intravenous immunoglobulin monotherapy for drug-induced hypersensitivity syndrome. Acta

Derm Venereol. 2012;92:100–1.
15. Moling O, Tappeiner L, Piccin A, Pagani E, Rossi P, Rimenti G, et al. Treatment of DIHS/DRESS syndrome with combined N-acetylcysteine, prednisone and valganciclovir – A hypothesis. Med Sci Monit. 2012;18:CS57–62.
16. Epomedicine. Steroid induced leukocytosis 2016 [updated 23 December 2016. Available from: https://epomedicine.com/medical-students/steroid-induced-leukocytosis/.
17. Subramaniam N, Mundkur S, Kini P, Bhaskaranand N, Aroor S. Subramaniam N, Mundkur S, Kini P, Bhaskaranand N, Aroor S. Clinicohematological study of thrombocytosis in children. ISRN Hematol. 2014;2014:389257.
18. Balakrishna J. Drug hypersensitivity 2018 [updated 30 July 2020; cited 2020 17 September]. Available from: http://www.pathologyoutlines.com/topic/lymphnodesdrughypersensitivity.html.
19. Uda H, Suga Y, Toriba E, Staub AY, Shimada T, Sai Y, et al. Multiday corticosteroids in cancer chemotherapy delay the diagnosis of and antimicrobial administration for febrile neutropenia: a double-center retrospective study. J Pharm Health Care Sci. 2019;5:3.