CASE REPORT

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A Rare, Fatal But Treatable Anti-tuberculosis Drug Reaction: A Case Report on DRESS Syndrome Secondary to Akurit-4

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ABSTRACT Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a severe spectrum of hypersensitivity condition which has been rarely reported to be induced by anti-tuberculosis medication. Here, we report a patient on Akurit-4 for pulmonary tuberculosis who developed fever and pneumonitis after six weeks of intensive treatment. Initially it was treated as infective cause and was started on intravenous antibiotics. However, the fever persisted and the patient subsequently developed maculopapular rash and lymphadenopathy, followed by progressive transaminitis, eosinophilia and lymphocytosis. DRESS syndrome induced by Akurit-4 was suspected, therefore the medication was discontinued and oral systemic steroids were given. The symptoms resolved and the abnormal laboratory investigations normalized after few weeks. The objective of this case report is to share an uncommon occurrence of Akurit-4-induced DRESS syndrome and to highlight the importance of recognising it early as, it is a potentially treatable condition despite being highy mortal.

Keywords: DRESS syndrome; tuberculosis; exanthema; eosinophilia; lymphocytosis

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a potentially life-threatening form of hypersensitivity condition triggered by exposure to certain drugs, commonly aromatic anti-convulsant, sulpha derivates, antidepressants, nonsteroidal anti-inflammatory drugs, and certain antimicrobials.[1] Rarely it can be triggered by anti-tuberculosis medication as observed in the patient reported in this article. DRESS syndrome is characterized by fever, maculopapular skin rash, lymphadenopathy, haematological abnormalities such as thrombocytopenia, eosinophilia and lymphocytosis, and variable internal organ involvement such as liver, kidney, heart and lungs. The onset is typically between 2 to 8 weeks after drug exposure. The mainstay of treatment is prompt identification of the signs and symptoms, rapid withdrawal of the offending drug, and commencement of systemic steroids if indicated in severe cases. DRESS syndrome has a mortality rate up to 10 to 20%. Therefore, it is imperative to avoid diagnostic delay as it can cause detrimental consequences to the patient.

CASE REPORT

A 15-year old boy who was diagnosed with smear positive pulmonary tuberculosis (TB) and was started on anti-TB treatment in the form of 2 tablets

daily of Akurit-4 (Rifampicin 150 mg, Isoniazid 75 mg, Pyrazinamide 400 mg, Ethambutol 275 mg) was presented on the 6th week of the intensive phase of his anti-TB treatment with fever and myalgia for a few days. His vital signs were stable, and systemic examinations were unremarkable except for reduced vesicular breath on the base of the left lung. Initial blood examinations were done (Table 1). He was treated with diagnosis of viral fever and was admitted for observation. On day 6 of admission, he developed a high-grade fever. His chest symptom was worsening, and chest X-ray showed signs of pneumonitis with unchanged cavitating lesion (Figure 1). Than contrast-enhanced computed tomography scan of the thorax was obtained and it showed thick-walled cavitating lesion with associated lung nodule, bronchiectatic changes, tree in bud appearance and mediastinal lymphadenopathy. It also showed findings consistent with tuberculosis (Figure 2). He was started intravenous (IV) ceftriaxone 1 g once daily in addition to Aquarit-4 to cover for infective pneumonitis, which later was switched to IV tazobactam 500 mg and piperacillin 4 g quid after 3

TABLE 1: Initial blood investigations taken during admission which shows leukopenia and thrombocytopenia.

Investigations	Result	Normal Range
Haemoglobin	13.4 g/dL	13.5-17.4 g/dL
White cell count	3.7x10^9/L	4.1-11.4x10^9/L
Neutrophil	1.7x10^9/L	3.9-7.1x10^9/L
Lymphocytes	1.5x10^9/L	1.8-4.8x10^9/L
Eosinophils	0.1x10^9/L	0.0-0.8x10^9/L
Platelet	117x10^9/L	142-350x10^9/L
Alanine aminotransferase	26 U/L	0-55 U/L
Bilirubin	4.8 umol/L	3.4-20.5 umol/L
Alkaline phosphatase	92 U/L	40-150 u/L
Albumin	32 g/L	35-50 g/L
Sodium	136 mmol/L	136-145 mmol/L
Potassium	4.2 mmol/L	3.5-5.1 mmol/L
Urea	3.2 mmol/L	3.2-7.4 mmol/L
Creatinine	78 umol/L	63.6-101.5 umol/L
Dengue NS-1 and IgM antibody	Negative	
C-Reactive Protein	1.79 mg/dL	<0.5 mg/dL

C-Reactive protein was slightly elevated. Otherwise, the Dengue virus NS-1 antigen and IgM antibody test was negative, and other parameters were within normal range.

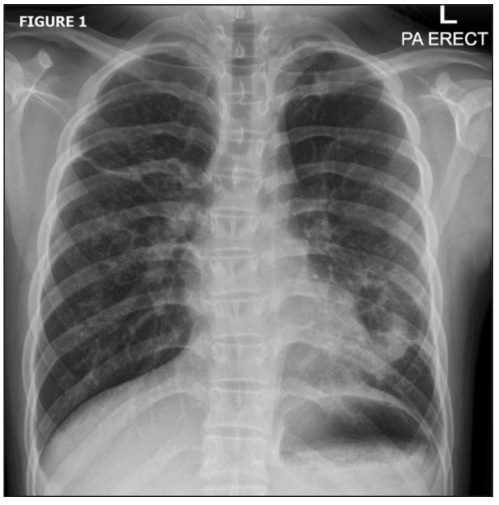

FIGURE 1: Radiograph imaging of the chest taken during admission which shows pneumonitis with cavitating lesions. The cavitation was reported unchanged compare to previous image, which is not shown in this case report.

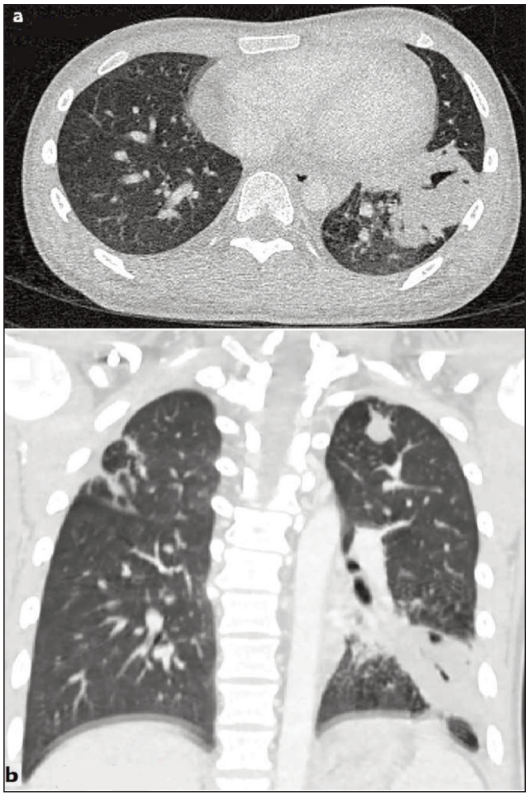

FIGURE 2: a) Transverse view of computed tomography of thorax shows multiple thick-walled cavitating lesions seen in the apicoposterior segment of the left upper lobe and left lower lobe. Few smaller lung nodules are seen in the apicoposterior segment of right upper lobe and left lower lobe. There are associated bronchiectatic changes with tree in bud appearances in the left lower lobe and the apicoposterior segment of left upper lobe. Fibrotic changes seen in the apical and anterior segments of the right upper lobe, left upper and lower lobes; **b)** Coronal view.

days as there was no improvement. Subsequently, he developed transaminitis, and also a maculopapular rash which started over the neck region and moved down to the trunk and both lower limbs with total of 40% body surface area involved. Drug rash was suspected and the IV antibiotic was discontinued. However, despite discontinuing the antibiotics, the rash persisted and his blood examinations showed worsening transaminitis and increasing trend of eosinophilia and lymphocytosis (Table 2). Under the light of the haematological abnormalities in addition to transaminitis and pneumonitis which signify multiorgan involvement, drug reaction with eosinophilia and systemic symptoms syndrome secondary to the Akurit-4 was suspected. Therefore, the Akurit-4 was discontinued, and oral prednisolone 25 mg once daily was started. The fever and maculopapular rash subsided. Later on, he was given second line anti-tuberculosis treatment which contained streptomycin, ethambutol and moxifloxacin. At the time of discharge, the patient was clinically well and the haematological abnormalities slowly returned to normal. The oral prednisolone dose was gently tapered down 5 mg every week.

DISCUSSION

Anti-tuberculosis drugs are known to cause several side effects, such as peripheral neuropathy, liver toxicity, optic neuritis, precipitation of gout, just to name a few. It also known to cause hypersensitivity reaction in some patients. However, it is not common to cause hypersensitivity reaction with multi organ involvement, a syndrome that is called drug reaction with eosinophilia and systemic symptoms (DRESS). DRESS syndrome is a potentially life-threatening hypersensitivity condition that usually not expected and presents within 8 weeks of initiation of the causative medication. Aromatic anticonvulsants such as phenytoin, phenobarbital and carbamazepine are the most common triggers, but other drugs such as allopurinol, minocycline, dapsone, sulfasalazine, and mexiletine have also been reported to be associated with DRESS syndrome. Fever is the most common feature and may precede the skin eruption.[2] Skin eruption starts as a morbilliform rash that progresses to confluent, diffuse and generalised erythroderma with follicular attenuation. The face and upper part of the trunk and extremities are involved first. Periorbital and facial oedema occur in 25% of the cases and is usually symmetrical, persistent and associated with erythema and nearly half of the patients have inflammation and pain of mucous membrane most often the mouth or pharynx and does not progress to erosion. In DRESS syndrome, the eruption typically involves more than 50% of the body surface area. Haematological abnormalities are found in 50% of the cases and include thrombocytopaenia, eosinophilia, leucocytosis, haemolytic anaemia and atypical lymphocytes. Internal organ involvement includes elevated liver enzymes, hepatitis and liver necrosis and other fatal complications such as pericarditis, pneumonitis, nephritis, pancreatitis, colitis, myositis and meningitis are also seen.[3]

TABLE 2: Blood investigations trend throughout admission from initial presentation which shows progressive worsening of Alanine aminotransferase, and increasing numbers of eosinophils and lymphocytes.

Investigations	Result	Normal Range
Alanine aminotransferase	26>68>118>217>324 (U/L)	0-55 U/L
Eosinophils	0.7>0.8>1.3 (x10^9/L)	0.0-0.8x10^9/L
Lymphocytes	4.5>6.3 (x10^9/L)	1.8-4.8x10^9/L

Treatment of DRESS syndrome generally includes withdrawal of the offending drugs, correction of electrolyte imbalance, and administration of steroid. High potency topical corticosteroid can be given for symptomatic relieve in the patients without organ involvement. In those with organ involvement, systemic corticosteroids have become a mainstay of therapy in the form of prednisolone. It often produces dramatic improvement in clinical symptoms and laboratory measures in just a few days after the initiation of treatment.[4] The prednisolone dose will be tapered down slowly over course of 8 to 12 weeks as rapid tapering may increase the risk of relapse. If symptoms continue to progress despite the use of corticosteroids, other options include intravenous immunoglobulin or plasmapheresis.[5] Other non-steroidal immunosup-

pressive agents have been reported to show a promising treatment effectiveness.[6] However, further studies are required to establish the benefits of these immunosuppressants as the number of patients receiving these treatments is very limited. DRESS syndrome has mortality rate of around 10%.[7] The damage to organs can be severe and permanent. Fortunately, most affected patients will recover completely in weeks to months after causative drug withdrawal.[8]

The diagnosis of DRESS syndrome tends to be missed or delayed due to its highly variable presentation. Our patient developed DRESS syndrome at 6th week of his intensive phase of anti-tuberculosis treatment with Akurit-4 with the clinical manifestations of fever, pneumonitis, hepatitis and other deranged laboratory investigations that mimic those of a severe superimposed infection. As the patient did not respond to two types of intravenous antibiotics and also with the development of maculopapular rash and progressive transaminitis, eosinophilia and lymphocytosis, it raised the suspicion of DRESS syndrome. The patient showed a dramatic response to withdrawal of Akurit-4 and oral systemic steroids. Apart from the difficulty to recognize the syndrome, one other major challenge faced in managing this patient was the decision to withdraw the first line anti-tuberculosis treatment and the initiation of second line medication which fortunately the patient responded without any difficulty.

In conclusion, this case report served to share an uncommon occurrence of DRESS syndrome secondary to anti-TB medications, and to emphasize the importance of having high suspicion level to avoid diagnostic delay for this severe drug reaction which has significant mortality rate and potentially treatable with prompt withdrawal of the offending drugs and initiation of systemic steroids. However, clinical judgement has to be made from case to case basis in order to differentiate this condition from those caused by infections.

Informed Consent

Written informed consent was obtained from the patient in order to publish this case report.

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Conflict of Interest

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Authorship Contributions

Idea/Concept: *Azliza İbrahim;* ***Control/Supervision:*** *Alvin Oliver Payus;* ***Data Collection and/or Processing:*** *Azliza İbrahim;* ***Literature Review:*** *Alvin Oliver Payus;* ***Writing the Article:*** *Azliza İbrahim.*

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