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CASE REPORT

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Drug Reaction Syndrome with Eosinophilia and Systemic Symptoms (DRESS) Syndrome Associated with Anti-Tuberculosis Therapy: A Case Report

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ABSTRACT

Diagnosis of drug reaction syndrome with eosinophilia and systemic symptoms (DRESS), which is a rare condition, can be observed in patients undergoing therapy for tuberculosis. This particular side effect, associated with the consumption of an Anti-tuberculosis Drug (ATD), has been known to lead to fatal outcomes.

A 19-year-old male individual was diagnosed with pulmonary tuberculosis and started a 4-day treatment regimen comprising a fixed combination of ATD. Subsequent to the administration of the drugs, the patient experienced a severe skin reaction characterized by widespread erythematous macules with well-defined borders. The patient's condition improved after administration of Methylprednisolone at an intravenous daily dosage of 62.5 mg.

A preliminary assessment was conducted based on a previous report, indicating red patches on the body, increased white blood cell count, and elevated eosinophils after anti-tuberculosis medication. These findings align with a probable case of DRESS as per the Registry of Severe Cutaneous Adverse Reaction (RegiSCAR) scoring system.

Steroids show efficacy in treating DRESS when anti-tuberculosis drug therapy starts.

Keywords: DRESS, hypereosinophilia, antituberculous therapy

INTRODUCTION

Tuberculosis (TB) infection stands as the most prevalent infectious disease globally, affecting a staggering two billion individuals worldwide according to statistics from 2019, resulting in a mortality rate of 7.1 million. Consequently, TB emerges as the primary cause of death attributed to infections, with an escalating annual incidence rate that continues to rise. The management of tuberculosis necessitates the administration of multiple pharmacological agents to mitigate the development of resistance. However, the administration of each drug agent harbors the potential of eliciting adverse reactions that range from mild and tolerable to severe (1,2). Among the spectrum of rare side effects associated with the consumption of ATD, DRESS surfaces as a critical concern due to its potential lethality (3). This particular syndrome presents as a medical condition characterized by severe skin symptoms and the participation of internal organs. The fatality rate associated with this syndrome is approximately 10%. The precise occurrence of DRESS syndrome remains unclear, with predicted probabilities in the general population varying from 1 in 1,000 to 1 in 10,000 drug administrations (4).

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The pulmonary manifestation of DRESS manifests with a myriad of clinical presentations, encompassing mild symptoms like a persistent cough or dyspnea along with nonspecific interstitial alterations on chest imaging, to severe conditions such as acute respiratory distress syndrome (ARDS) that culminates in life-threatening hypoxic respiratory failure. In this study, we report a case of a patient diagnosed with DRESS due to ATD according to the RegiSCAR score (5).

CASE REPORT

A 19-year-old male patient presented at the Emergency Department owing to a progressive exacerbation of shortness of breath spanning over a period of four days. Prior to hospitalization, the patient endured recurrent episodes of fever for three weeks, the emergence of red and swollen lesions scattered across the body for three days, reduced appetite persisting for a month, and a lingering cough accompanied by difficulty in expectorating mucus for a duration exceeding one month (Figure 1, 2). Following admission, the individual received a prescribed regimen comprising a fixed combination of anti-tuberculosis medications. Subsequently, the patient developed a severe cutaneous reaction characterized by the presence of extensive erythematous macules demarcated by well-defined borders. Laboratory investigations unveiled findings indicative of leukocytosis coupled with hypereosinophilia (leukocytes 32,990/μl, eosinophils 48%), elevated levels of AST (269 U/L) and ALT (379 U/L), hypoalbuminemia, increased total bilirubin, and direct bilirubin. Additionally, the patient encountered episodes of oxygen desaturation necessitating the administration of FiO2 at 80%, with blood gas analysis revealing values of PH: 7.45 , PCO2: 30 mmHg, PO2: 91 mmHg, HCO3: 20.9, mmol/l BE: -3.1 mmol/l, and SO2: 95%. The patient underwent abdominal ultrasound with findings of cholecystitis, ascites, and bilateral minimal pleural effusion. The bronchoscopy carried out during the acute phase revealed hyperemia, while the results of the bronchoalveolar lavage were inconclusive, thereby eliminating the suspicion of acute eosinophilic pneumonia (Figure 3). Examination of the pathology revealed the presence of several lymphocytic inflammatory cells and some mesothelial cells. No specific pathological process or malignant cells were identified. According to the dermatovenerology expert's assessment, the patient did not need to undergo a patch test because clinically the patient can be assessed as DRESS. The patient's condition improved after administration of Methylprednisolone intravenously at a daily dosage of 62.5 mg (Figure 4).

DISCUSSION

DRESS syndrome represents a severe form of cutaneous adverse reactions (SCARs) triggered by pharmaceuticals. The identification of DRESS syndrome is frequently disregarded or overlooked due to its diverse and intricate symptoms (4). Diagnosis commonly hinges on the

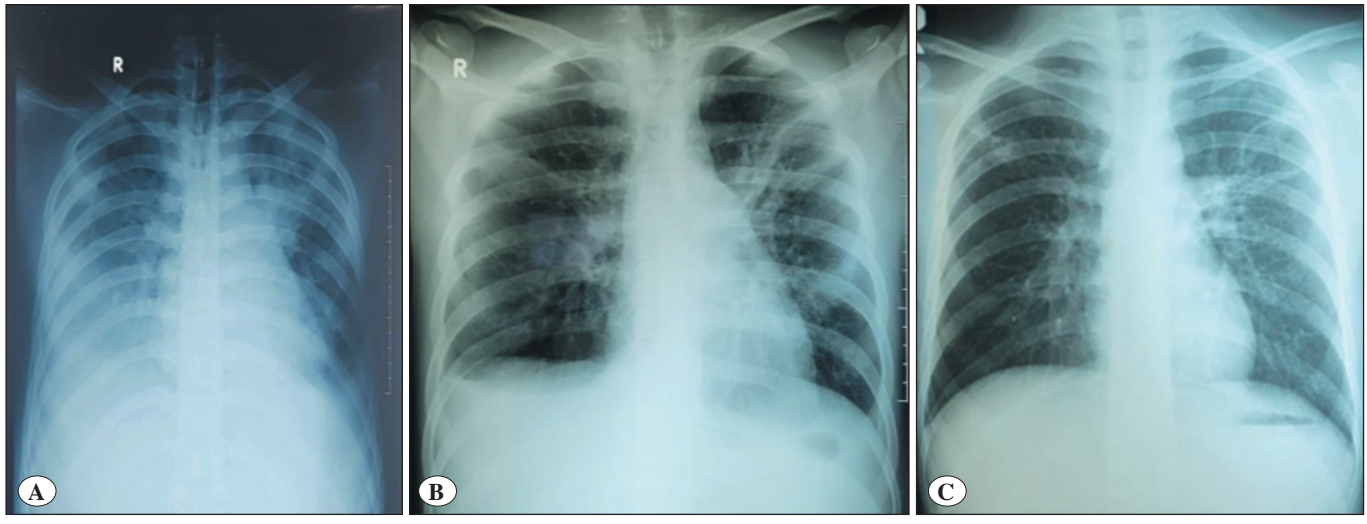

Figure 1. Serial chest photo On the first day of admission to the Emergency Room, a chest radiograph showed uniform opacity in the lower one-third of the right hemithorax and fibro infiltrates in both lung fields **(A)**. The subsequent chest radiograph taken on day 8 during treatment indicated that the patient received ATD regimen consisting of streptomycin, levofloxacin, ethambutol, and intravenous steroid administration **(B)**. The patient's follow-up image was taken 16 days after confirming the diagnosis **(C)**.

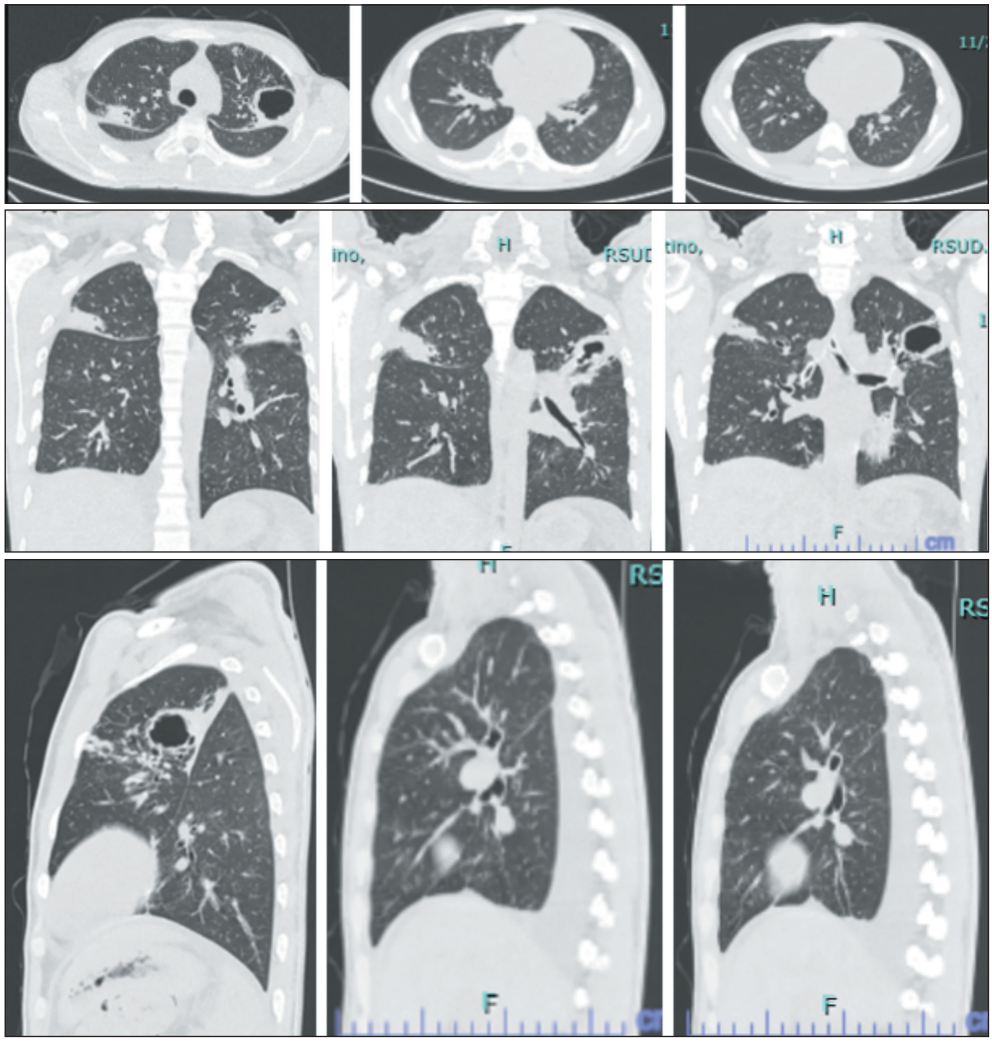

Figure 2. HRCT shows pulmonary tuberculosis with right pleural effusion, bilateral upper paratracheal lymphadenopathy, and left peribronchial lymphadenopathy.

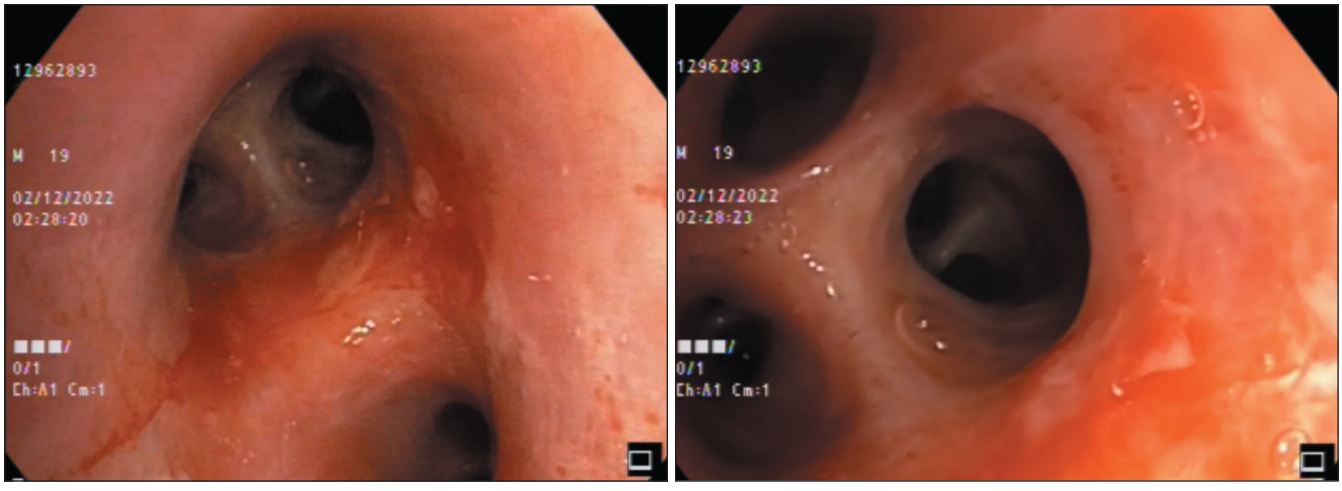

Figure 3. Bronchoscopy performed during the acute phase showed hyperemia, and the results of the bronchoalveolar lavage were inconclusive, thus ruling out the suspicion of acute eosinophilic pneumonia.

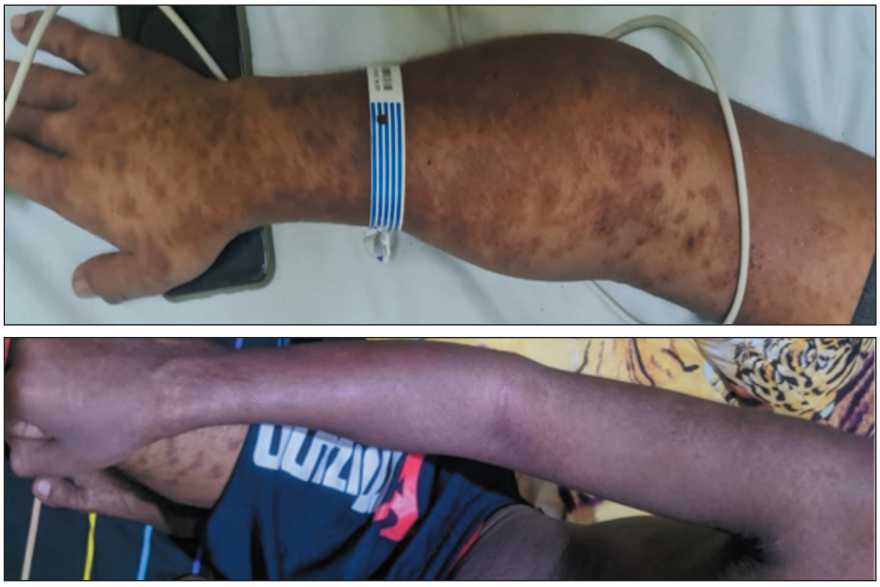

Figure 4. Clinical changes observed in the patient post therapy include multiple erythematous macules-plaques, lenticular-plaques with well-defined borders, accompanied by scaling (+), and the presence of dark crusts (+) on various lesions. Assessment following the cessation of anti-tuberculosis treatment (ATD) and the initiation of steroids and other symptomatic therapies.

patient's medical background and clinical assessments, which reveal extensive red patches on the skin, elevated white blood cell count, and heightened eosinophil levels subsequent to the usage of anti-tuberculosis medications (6).

The etiology of DRESS remains incompletely elucidated. Interleukin (IL)-33 may be discharged by compromised epithelial cells following exposure to deleterious agents such as allergens, infectious agents, and various inhaled toxins like tobacco smoke. The production and subsequent attachment of IL-33 to cells expressing its receptor (ST2), for instance, macrophages and dendritic cells, can result in the recruitment and stimulation of T-helper cell type 2 (Th2)-skewed T lymphocytes and the synthesis of cytokines such as IL-5, which further facilitates the recruitment and activation of eosinophils in pulmonary tissue. Eosinophils might also migrate to the lungs due to chemokine gradients and heightened permeability in the setting of endothelial damage. Eosinophils are additionally implicated in diverse inflammatory reactions and can modulate innate and adaptive immunity. The primary stimulants in DRESS that trigger and attract eosinophils are IL-5 and eotaxin. In conjunction with IL-5, eotaxin-1 has been recognized as a remarkably specific and potent attractant for eosinophils. Based on the aforementioned details, the individual under consideration exhibited manifestations consistent with a confirmed diagnosis of DRESS. Symptoms included fever, lymphadenopathy, elevated eosinophils, cholecystitis, ascites, and a rash indicative of DRESS. Findings from screenings for hepatitis A, B, C, ANA, and blood cultures returned negative results. Upon evaluation of the cumulative score, the individual had amassed a total of 7 points, meeting the criteria for a definitive instance of DRESS. In accordance with the diagnosis, the individual fulfilled five of the seven specified criteria for DRESS, denoting a variant presentation of this syndrome. Mild cases of DRESS syndrome can be managed with topical corticosteroids, while severe symptoms necessitate systemic corticosteroid therapy to address substantial impairment of vital organs like the heart, lungs, or liver (3,6).

Lung participation represents the third most frequently encountered form of organ involvement observed in DRESS syndrome, manifesting in roughly one-third of DRESS patients. The pulmonary engagement can manifest with compromised lung functionality, interstitial pneumonitis, pleuritis, and acute respiratory distress syndrome. The association between pulmonary involvement and minocycline usage has been documented. The majority of instances involving pulmonary participation exhibit satisfactory recovery, apart from a minority requiring mechanical ventilation due to acute respiratory distress syndrome (4,6,7).

The diagnostic approach to be employed in cases where there is a suspicion of DRESS syndrome involves a specific sequence of actions. Firstly, it is recommended to cease the offending culprit drug (ATD) if feasible. Subsequently, a patch test should be conducted, ideally scheduled at a

Table I: These clinical manifestations correspond to the likelihood of DRESS cases according to the Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) scoring system.

Criteria	score			Patient	add
	-1	0	1		
Fever ≥ 38,5^{0}C	N/U	Y		1	T: 38.7 ^{0}C
Enlargement of lymph nodes		N/U	Y	1	Lymphadenopathy in the right and left upper paratracheal areas and left peribronchial area
Eosinophilia ≥ 0,7 x 10^9/L or ≥10% if WBC <4,0x10^9/L		N/U	Y	1	Eosinophilia ≥ 1,5 x 10^9/L or ≥ 20% if WBC < 4,0 x10^9/L
Atypical lymphocytosis		N/U	Y	0	Inflammatory lymphocytes and some mesothelial cells.
Skin rash					Rash suggestive of DRESS: ≥2 symptoms: purpuric lesions (except lower limbs), infiltration, facial edema, psoriasiform desquamation
Extent >50% of Body Surface Area (BSA)		N/U	Y	1	
Rash suggestive of DRESS	N	U	Y	1	
Skin biopsy indicating DRESS	N/U	Y		-1	
Organ involvement		N	Y	1	Score 1 point for each organ involvement, maximum score: 2
Resolusi ruam ≥15 hari	T/TD	Y		0	Terjadi perbaikan (≥15 hari)
Eksklusi penyebab lain		T/TD	Y	1	Skor 1 jika 3 tes berikut dilakukan dan hasilnya semua negatif: HAV, HBV, HCV, Mycoplasma, Klamidia, ANA, kultur darah

Total score: < 2 points: no case; 2–3 points: possible case; 4–5 points: probable case; > 5 points: confirmed case.

ANA: Antinuclear antibodies, **BSA:** Body surface area, **HAV:** Hepatitis A virus, **HBV:** Hepatitis B virus, **HCV:** Hepatitis C virus, **T:** No, **TD:** Not determined, **WBC:** White blood cells, **Y:** Yes.

minimum of one month post-recovery from the DRESS episode. This patch test serves the purpose of providing valuable guidance on the optimal sequence for reintroducing the offending drug (ATD) into the patient's treatment regimen (3,8).

A notable improvement was observed subsequent to the initiation of treatment with intravenous Methylprednisolone, administered at a dosage of 62.5 mg on a daily basis over a period of three days. This improvement was evident both clinically, through the patient's physical presentation, and radiologically, based on the diagnostic imaging findings (5,8) (Table I).

CONCLUSION

DRESS syndrome is a potential side effect of anti-tuberculosis therapy. Its incidence is not well-known but can be fatal. Accurate diagnosis of DRESS syndrome can expedite its management. Steroids have been proven effective in managing DRESS when initiated alongside anti-tuberculosis drug therapy. A positive response to steroid treatment suggests inflammation rather than infection is involved in the case. Reintroduction of anti-tuberculosis therapy can be considered if the condition is managed appropriately, allowing the patient to complete TB treatment. However, our patient himself has not yet reintroduced ATD because the patient refused to continue the evaluation.

Conflict of Interest

Authors declare no conflict of interest.

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Ethical Approval

Ethical approval was not required for this case report, however written informed consent was obtained from the patient and is available for review under request.

Authorship Contributions

Concept: **Nurul Atika,** Design: **Nurul Atika, Richar Tomy Thendeyas,** Data collection or processing: **Nurul Atika, Garinda Alma Duta,** Analysis or Interpretation: **Nurul Atika, Garinda Alma Duta, Arief Bakhtiar,** Literature search: **Nurul Atika, Garinda Alma Duta, Arief Bakhtiar, Richar Tomy Thendeyas,** Writing: **Nurul Atika,** Approval: **Garinda Alma Duta, Arief Bakhtiar, Richar Tomy Thendeyas.**

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