Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome may be a life-threatening condition that is precipitated by exposure to various therapeutic agents. DRESS syndrome after exposure to isoniazid is rare and relevant literature in children is scarce. We report a young boy with tuberculosis who developed DRESS syndrome after exposure to isoniazid. A 9-year-old boy, diagnosed clinically as pulmonary tuberculosis, presented with fever, fast breathing, maculopapular rash, and one episode of gross hematuria. He had been on 4-drug ATD therapy (isoniazid, rifampicin, ethambutol, and pyrazinamide) for the past 4 weeks. In view of multiorgan involvement and absence of a microbiological diagnosis of tuberculosis, vasculitis was considered and he was treated with steroids. As the child recovered, both corticosteroids and ATD therapy were stopped. At 6 months of follow-up, he was presented with pneumonia. Microbiological diagnosis of tuberculosis was made and 4-drug ATD therapy was reintiated. After 15 days, he again developed a high-grade fever and rash. On evaluation, isoniazid-induced DRESS syndrome was diagnosed. Subsequently, he received a modified regimen of ethambutol, pyrazinamide, levofloxacin, and linezolid. DRESS syndrome did not recur on these ATDs and the child became asymptomatic. Linezolid was stopped after 3 months of therapy and ethambutol, pyrazinamide, and levofloxacin are being continued. Currently, he has completed 15 months of modified ATD therapy. As a high index of suspicion is required for early diagnosis and management that are crucial to reducing morbidity and mortality, DRESS syndrome should be among the differentials in children with unexplained febrile illnesses.

Keywords: DRESS, eosinophilia, isoniazid, steroid, tuberculosis, vasculitis

Case Presentation

A 9-year-old boy presented to a local primary healthcare facility with a 3-month history of fever and cough. He was diagnosed to have TB based on Mantoux positivity (14 mm) and was initiated on 4-drug ATD therapy (isoniazid, rifampicin, ethambutol, and pyrazinamide). However, 4 weeks following ATDs, he developed fever, fast breathing, maculopapular rash, and one episode of gross hematuria. He was admitted to a local hospital for 3 weeks DRESS syndrome due to first-line antitubercular therapy – A diagnostic imbroglio!

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Abstract

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome after the use of first-line antitubercular drugs (ATDs) is rare and literature regarding DRESS syndrome due to ATDs is scarce in children. We report a young boy with tuberculosis who developed DRESS syndrome after exposure to isoniazid. A 9-year-old boy, diagnosed clinically as pulmonary tuberculosis, presented with fever, fast breathing, maculopapular rash, and one episode of gross hematuria. He had been on 4-drug ATD therapy (isoniazid, rifampicin, ethambutol, and pyrazinamide) for the past 4 weeks. In view of multiorgan involvement and absence of a microbiological diagnosis of tuberculosis, vasculitis was considered and he was treated with steroids. As the child recovered, both corticosteroids and ATD therapy were stopped. At 6 months of follow-up, he was presented with pneumonia. Microbiological diagnosis of tuberculosis was made and 4-drug ATD therapy was reintiated. After 15 days, he again developed a high-grade fever and rash. On evaluation, isoniazid-induced DRESS syndrome was diagnosed. Subsequently, he received a modified regimen of ethambutol, pyrazinamide, levofloxacin, and linezolid. DRESS syndrome did not recur on these ATDs and the child became asymptomatic. Linezolid was stopped after 3 months of therapy and ethambutol, pyrazinamide, and levofloxacin are being continued. Currently, he has completed 15 months of modified ATD therapy. As a high index of suspicion is required for early diagnosis and management that are crucial to reducing morbidity and mortality, DRESS syndrome should be among the differentials in children with unexplained febrile illnesses.

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where he received mechanical ventilation for the initial 9 days. The treating physicians suspected vasculitis owing to multiorgan involvement. He was treated with 3 doses of intravenous methylprednisolone pulse (IVMP) therapy. Following IVMP, oral prednisolone at 2 mg/kg was initiated and ATD therapy was continued. He was subsequently referred to our institute.

On reviewing the investigations done earlier, the complete blood counts showed leucocytosis (up to 30.0 × 10⁹/L [normal <15.0 × 10⁹/L]) with eosinophilia (absolute count: 1.8 × 10⁹/L [normal <0.5 × 10⁹/L]). Urine examination showed hematuria and albuminuria. The chest radiograph showed bilateral diffuse infiltrates, which had improved significantly [Figure 1] after glucocorticoid therapy. Antinuclear (ANA) and antineutrophil cytoplasmic antibodies (ANCA) were negative. His serum IgE levels were elevated (4,064 kIU/L [normal <50]). On examination, he had hypertension (126/80 mmHg), cushingoid facies, maculopapular rash over the face, trunk, and extremities, and hepatomegaly. Investigations [Supplementary Table 1] showed thrombocytosis (444 × 10⁹/L [normal <400]), microscopic hematuria, and mild elevations of urinary protein-creatinine ratio (0.38 [normal <0.2]) and alanine aminotransferase (97 U/L [normal <40]). The autoantibody profile (ANA, ANCA, anti-glomerular basement membrane antibody, and anti-dsDNA) and a detailed parasitology/infectious/immune workup were negative. Chest radiograph was unremarkable and abdominal ultrasound was normal. Chest imaging showed large areas of consolidation in the left upper, lingular, and lower lobes [Figure 2]. The laryngoscopic examination was suggestive of tubercular laryngitis. Repeat gastric lavage showed positivity for acid-fast bacilli (on multiple occasions) and the cartridge-based nucleic acid amplification test was positive for Mycobacterium tuberculosis, which was sensitive to isoniazid and rifampicin. Lung aspiration showed necrotic epithelioid granulomas with positivity for acid-fast bacilli. A diagnosis of TB was made and he was commenced on 4-drug ATD therapy (isoniazid, rifampicin, ethambutol, and pyrazinamide). After 15 days of ATD therapy, he developed a maculopapular, pruritic rash distributed over the face, trunk, and extremities [Figure 3]. It was also accompanied by a continuous high-grade fever without any other specific focus.

Repeat laboratory evaluation [Supplementary Table 3] showed eosinophilia (12.0%, absolute count: 1,666 × 10⁹/L), elevated serum alanine and aspartate aminotransferases of 240 and 279 U/L, respectively, which increased to 307 and 397, respectively, over the next 4 days. The presence of fever, rash, systemic manifestations and eosinophilia aroused the suspicion of DRESS syndrome. Skin biopsy was consistent with DRESS syndrome [Supplementary Figure 1] and evaluation for other potential causes was negative [Supplementary Table 3]. The ATDs were discontinued and tapering doses of oral prednisolone were administered (initially at 2 mg/kg/day) resulting in clinical improvement. To identify the culprit, ATDs were reintroduced one by one. He again developed a fever and maculopapular rash once isoniazid was initiated. Subsequently, a modified regimen of ethambutol, pyrazinamide, levofloxacin, and linezolid was initiated gradually. DRESS syndrome did not recur on these ATDs and he became completely asymptomatic. Linezolid was stopped after 3 months of therapy and ethambutol, pyrazinamide, and levofloxacin were continued. Although the index child continued to remain asymptomatic, follow-up imaging showed a large pneumatocele in the left upper and lingular lobes resulting in compression-collapse of adjacent lung parenchyma. The pneumatocele was drained successfully via a percutaneous pigtail catheter placed under radiological guidance [Supplementary Figure 2]. Currently, he has completed 15 months of modified ATD-therapy and is doing well.

Discussion

DRESS syndrome due to ATDs is rare and only a few reports are available in the pediatric literature. In a systematic review, Metterle et al. showed that the leading therapeutic agents causing DRESS syndrome were anticonvulsant drugs.
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The mean duration of drug exposure at symptom onset was 24 days. Among ATDs, rifampicin is the most common agent implicated for DRESS syndrome. However, isoniazid, ethambutol, pyrazinamide, and fluoroquinolones have also been implicated. It may be difficult to identify the culprit drug at the beginning as first-line ATDs are mostly prescribed in combination. The common clinical manifestation of DRESS includes skin rash (morbilliform), fever, lymphadenopathy, liver dysfunction, leukocytosis, and eosinophilia. However, the difficulty arises when systemic symptoms are present without any cutaneous manifestations. The RegiScar or the Japanese criteria help establish the diagnosis. The total RegiScar score in our patient was more than 5, fulfilling the criteria for a definitive case of DRESS syndrome [Supplementary Table 4]. As our child had systemic symptoms each time after isoniazid was reintroduced, we considered it to be the culprit drug. Rifampicin was avoided as being the most common ATD implicated to cause DRESS syndrome. There was no adverse reaction to ethambutol, pyrazinamide, levofloxacin, and linezolid in the index child.

Although identification of the culprit drug is based on the temporal correlation of symptoms with drug exposure, patch and lymphocytic transformation tests may be valuable adjunctive tools. Inability to perform these tests (due to availability constraints) may be an important limitation in our case; however, the strong temporal correlation (on multiple occasions) asserted the diagnosis of isoniazid-induced DRESS syndrome in our case.

Ethical approval and informed consent
As this manuscript pertains only to a case report, specific ethics approval is not mandated. Informed consent was taken from the parents of the child before inclusion into the manuscript.

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Conflicts of interest
There are no conflicts of interest.

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Supplementary Table 1: Laboratory investigations at first presentation to us

| Parameter                                      | Result                           |
|------------------------------------------------|----------------------------------|
| Hemoglobin (g/L)                               | 11.8 (11.5-15.5)                 |
| Total leukocyte count (×10⁹/L)                 | 8.62 (5.0-14.5)                  |
| Differential leukocyte count                   | N₉,Lₑ,Mₑ,Bₑ                   |
| Platelets (×10⁹/L)                             | 444 (150-400)                   |
| Serum urea (mg/dL)                            | 23 (10-50)                      |
| Serum creatinine (mg/dL)                       | 0.13 (0.5-1.2)                  |
| Total serum bilirubin (mg/dL)                  | 0.6 (<1.0)                      |
| Alanine aminotransferase (U/L)                 | 97 (5-45)                       |
| Aspartate aminotransferase (U/L)               | 37 (15-50)                      |
| Alkaline phosphatase (U/L)                     | 118 (145-420)                   |
| Total serum protein (mg/dL)                    | 6.6 (6.4-8.3)                   |
| C-reactive protein (mg/L)                      | 0.058 (0-3.5)                   |
| Total serum albumin (mg/dL)                    | 3.8 (3.5-5.6)                   |
| Urine routine microscopy                       | 120-125 RBCs/HPF                |
| Repeat urine microscopy                        | Normal                           |
| Urinary spot protein creatinine ratio          | 0.378 (<0.2)                    |
| Prothrombin time (seconds)                     | 10.2 (10-14.6)                  |
| International normalized ratio                 | 0.84                             |
| Activated partial thromboplastin time (seconds)| 26.5 (26-39)                    |
| Plasma fibrinogen (g/L)                        | 1.75 (1.89-4.75)                |
| Serum ferritin (ng/mL)                         | 38.74 (30-40)                   |
| Serum N-terminal pro-B type natriuretic peptide (pg/mL) | 183.4 (0-125)          |
| Hepatitis B surface antigen                    | Negative                         |
| Antihepatitis C virus IgM antibody             | Negative                         |
| Human immunodeficiency virus serology          | Negative                         |
| Antistreptolysin O (IU/mL)                     | 44.2 (<200)                     |
| Gastric lavage for acid-fast bacilli           | Negative                         |
| Gastric lavage for Mycobacterial tuberculosis CB-NAAT | Negative                      |
| Filaria, Toxocara, and Toxoplasma serology     | All negative                     |
| Antinuclear antibody (IIF)                     | Negative                         |
| Antineutrophil cytoplasmic antibody (ELISA for MPO/PR3) | Both negative                  |
| Antiglomerular basement membrane antibody      | Negative                         |
| Antidouble stranded DNA antibody (IU/mL)       | 18 (<60)                        |
| Antitissue tranigluminate IgA antibody (EliA U/mL) | <0.1 (<7)                     |
| Gastric lavage for hemosiderin laden macrophages | Negative                      |
| Complement C3 (mg/dL)                         | 125.7 (78.9-178.9)              |
| Complement C4 (mg/dL)                         | 16.2 (14.5-61.6)                |
| CD3⁺ T cells [% of lymphocytes]                | 75.7 (60-76)                    |
| CD19⁺ B cells [% of lymphocytes]               | 15.7 (13-27)                    |
| CD16⁺ CD56⁺ NK cells [% of lymphocytes]        | 2.72 (4-17)                     |
| Absolute no. of CD3⁺ T cells (× 10⁹/L)        | 2.474 (1.200-2.600)             |
| Absolute no. of CD19⁺ B cells (× 10⁹/L)       | 0.514 (0.270-0.860)             |
| Absolute no. of CD16⁺ CD56⁺ NK cells (×10⁹/L)| 0.089 (0.100-0.480)             |
| IgG (g/L)                                      | 14.04 (7.72-17.71)              |
| IgA (g/L)                                      | 1.10 (0.73-2.09)                |
| IgE (kIU/L)                                    | 572 (0-78)                      |

Abnormal values are highlighted in bold. CB-NAAT, cartridge-based nucleic acid amplification test; ELISA, enzyme-linked immunosorbent assay; HPF, high-power field; IIF, indirect immunofluorescence; MPO, myeloperoxidase; RBCs, red blood cells; PR3, proteinase 3

Supplementary Figure 1: (a and b) Skin biopsy from the sites of rash showing flattening of rete ridges, spongiosis with focal basal cell vacuolization, and reactive Langerhans cell proliferation in the epidermis. The dermoepidermal junction is obscured by the upper dermal accompanied by lymphomononuclear infiltrate with exocytosis. These features are consistent with the diagnosis of DRESS syndrome.
### Supplementary Table 2: Laboratory investigations at 6 months of follow-up

| Parameter                                      | Result           |
|------------------------------------------------|------------------|
| Hemoglobin (g/L)                               | 9.9 (11.5-15.5)  |
| Total leukocyte count (<10⁹/L)                 | 10.7 (5.0-14.5)  |
| Differential leukocyte count                   | N₅₋₁₀₅₋₁₀ M₄₋₁₀ B₃₋₁₀ |
| Platelets (<10⁹/L)                             | 447 (150-400)    |
| Serum urea (mg/dL)                             | 15 (10-50)       |
| Serum creatinine (mg/dL)                       | 0.29 (0.5-1.2)   |
| Total serum bilirubin (mg/dL)                  | 0.54 (<1.0)      |
| Alanine aminotransferase (U/L)                 | 8 (5-45)         |
| Aspartate aminotransferase (U/L)               | 20 (15-50)       |
| Total serum protein (mg/dL)                    | 7.3 (6.4-8.3)    |
| Total serum albumin (mg/dL)                    | 3.3 (3.5-5.6)    |
| Urine routine microscopy                       | Normal           |
| Repeat urine microscopy                        | Normal           |
| Urinary spot protein creatinine ratio          | 0.1 (<0.2)       |
| Prothrombin time (seconds)                     | 12.4 (10-14.6)   |
| International normalized ratio                 | 1.02             |
| Activated partial thromboplastin time (seconds)| 38.2 (26-39)     |
| Plasma fibrinogen (g/L)                        | 4.51 (1.89-4.75) |
| Gastric lavage for acid-fast bacilli           | Positive: 10-15/HPF |
| Gastric lavage for Mycobacterial tuberculosis  | Positive         |
| CB-NAAT                                        |                  |
| Gastric lavage for mycobacterial culture       | M. tuberculosis   |
| Urine for acid-fast bacilli                    | Negative         |
| Urine for Mycobacterial tuberculosis CB-NAAT    | Negative         |
| Urine for mycobacterial culture                | Negative         |
| Transthoracic echocardiography                 | Normal           |

*Abnormal values are highlighted in bold. CB-NAAT, cartridge-based nucleic acid amplification test; HPF, high-power field.

### Supplementary Table 3: Laboratory investigations at the time of appearance of rash after initiation of isoniazid

| Parameter                                      | Result           |
|------------------------------------------------|------------------|
| Hemoglobin (g/L)                               | 9.1 (11.5-15.5)  |
| Total leukocyte count (<10⁹/L)                 | 13.88 (5.0-14.5) |
| Differential leukocyte count                   | N₅₋₁₀₅₋₁₀ M₄₋₁₀ B₃₋₁₀ |
| Absolute eosinophil count (<10⁹/L)             | 1.666 (0.05-0.50) |
| Platelets (<10⁹/L)                             | 402 (150-400)    |
| Total serum bilirubin (mg/dL)                  | 0.7 (<1.0)       |
| Alanine aminotransferase (U/L)                 | 240 (5-45)       |
| Aspartate aminotransferase (U/L)               | 279 (15-50)      |
| Total serum protein (mg/dL)                    | 6.3              |
| Total serum albumin (mg/dL)                    | 2.5 (3.5-5.6)    |
| Urine routine microscopy                       | Normal           |
| Urinary spot protein creatinine ratio          | 0.15 (<0.2)      |
| Prothrombin time (seconds)                     | 13.9 (12-14)     |
| International Normalized Ratio                 | 0.93             |
| Activated partial thromboplastin time (seconds)| 36 (28-40)       |
| Hepatitis B surface antigen                    | Negative         |
| Antihepatitis C virus IgM antibody             | Negative         |
| Human immunodeficiency virus serology          | Negative         |
| Anti-Epstein-Barr viral capsid antigen (IgM)   | Negative         |
| Parvovirus serology                            | Negative         |
| Antinuclear antibody (IIF)                     | Negative         |
| Antidouble stranded DNA antibody               | 43 (<60)         |
| Antineutrophil cytoplasmic antibody (ELISA for MPO/PR3) | Both negative |
| Complement C3 (mg/dL)                          | 141.0 (78.9-178.9) |
| Complement C4 (mg/dL)                          | 20.7 (14.5-61.6) |
| Ultrasonography of the abdomen                 | Enlarged liver, normal echotexture |

*Abnormal values are highlighted in bold. ELISA, enzyme-linked immunosorbent assay; IIF, indirect immunofluorescence; MPO, myeloperoxidase; PR3, proteinase 3.

### Supplementary Figure 2: Chest radiograph at 12 months of modified ATD therapy showing a large pneumatocele in left upper and lingular lobes resulting in compression-collapse of adjacent lung parenchyma (a). A percutaneous pigtail catheter placed under radiological guidance to drain the pneumatocele and improve expansion of adjacent lung parenchyma (b)
| Parameters                                      | Designated Score | Score initially | Score at diagnosis |
|------------------------------------------------|------------------|-----------------|--------------------|
| Fever ≥38.5 °C                                 | No/Unknown=−1    | 0               | 0                  |
|                                               | Yes=0            |                 |                    |
| Enlarged lymph nodes                           | No/Unknown=0     | 0               | 0                  |
|                                               | Yes=1            |                 |                    |
| Eosinophilia                                   | No=0             | 2               | 2                  |
| Absolute eosinophil count (<10⁷/L) or eosinophil percentage if total leukocyte count <4.0×10⁹/L | 0.70-1.499 or 10-19.9%=1 | 0 | 0 |
|                                               | >1.500 or >20%=2 |                 |                    |
| Atypical lymphocytes                           | No/Unknown=0     | 0               | 0                  |
|                                               | Yes=1            |                 |                    |
| Skin rash >50% of body surface area            | No/Unknown=0     | 0               | 1                  |
|                                               | Yes=1            |                 |                    |
| Skin rash suggesting DRESS                     | No=−1            | 1               | 1                  |
|                                               | Unknown=0        |                 |                    |
|                                               | Yes=1            |                 |                    |
| Skin biopsy DRESS                              | No/Unknown=−1    | −1              | 0                  |
|                                               | Yes=0            |                 |                    |
| Organ involvement                              | No/Unknown=0     | 2               | 1                  |
|                                               | One organ=1      |                 |                    |
|                                               | Two or more organs=2 |     |                    |
| Resolution ≥15 days                            | No/Unknown=−1    | 0               | 0                  |
|                                               | Yes=0            |                 |                    |
| Evaluation of other potential causes           | Yes=1            | 1               | 1                  |
| Total score                                    | Minimum=−2       | 5               | 6                  |
|                                               | Maximum=9        |                 |                    |

Note: Final score <2, no case; final score 2-3, possible case; final score 4-5, probable case; final score >5, definite case