**DRESS syndrome induced by imatinib**

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**ABSTRACT**

Drug rash with eosinophilia and systemic symptoms (DRESS syndrome) is a severe, potentially life-threatening drug-induced hypersensitivity reaction characterized by cutaneous eruptions, fever, diffuse lymphadenopathy, along with eosinophilia and elevated liver enzymes. The severity and potential organ damage associated with DRESS mandates withdrawing the offending drug and provide a suitable replacement. We report a 55-year-old man who developed prolonged fever, generalized maculopapular rash and facial edema after 3 weeks of starting imatinib for chronic myeloid leukemia (CML). A diagnosis of DRESS was confirmed by eosinophilia and skin biopsy findings, along with a consistent RegiSCAR score. Imatinib was stopped and he was initiated on low-dose steroids, which led to complete resolution of rash and eosinophilia. A rechallenge with imatinib was positive, and he was switched to dasatinib for further therapy, following which he attained an optimal molecular response. DRESS following imatinib has only been reported in eight patients so far. In this report we summarize the current evidence for managing DRESS and its impact on the treatment of CML.

**KEY WORDS:** Chronic myelogenous leukemia, DRESS syndrome, drug reaction, imatinib

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**Introduction**

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare adverse drug reaction characterized by a triad of fever, skin rash, and internal organ involvement, reported in association with several drugs such as the aromatic antiepileptic drugs, dapsone, sulfasalazine, allopurinol, and antibiotics.\(^1\) It develops 2–6 weeks after the initiation of drug administration, and the initial symptoms are usually fever and maculopapular (MP) rash that may progress to exfoliative dermatitis. Lymphadenopathy, hepatitis, renal dysfunction, and hematologic abnormalities are observed to varying degrees, and it is often associated with considerable morbidity and mortality.\(^1,2\) However, diagnosis is occasionally challenging owing to its broad clinical spectrum due to multiorgan involvement.\(^2\) Prompt recognition and discontinuation of the culprit drug is the essential first step in the therapeutic approach to DRESS.

Imatinib is a first generation tyrosine kinase inhibitor (TKI) which is the preferred first line therapy for chronic myelogenous leukemia (CML) with a long-term survival exceeding 90%. Imatinib is known to be associated with several mild dermatologic reactions, most commonly a dose-dependent MP rash.\(^1\) However, in a small number of patients, it can potentially lead to serious cutaneous adverse drug reactions such as DRESS, necessitating dose modification, or discontinuation of therapy. We here report a patient who presented with DRESS following imatinib and summarize the evidence for evaluation and management of the same.

**Case Report**

A 55-year-old man was referred to us after leucocytosis was detected on routine examination. His initial hemogram
revealed a hemoglobin of 9.3 g/dL, mean corpuscular volume of 59 fl, WBC count of 8.33 × 10^9/L, and platelet count of 442 × 10^9/L. Examination was significant for moderate splenomegaly (6 cm below the left costal margin). Bone marrow findings were consistent with CML and RT-PCR for BCR/ABL1 positive for the p210 transcript. Imatinib (400 mg) was initiated in December 2019 with a diagnosis of CML. After 10 days, he developed fever, which was intermittent and associated with anorexia. Fever continued for almost 3 weeks without any further etiology being defined. He presented with a skin rash after 4 weeks, associated with facial edema, and persistence of fever.

Cutaneous examination revealed a blanchable morbilliform skin rash with exfoliation over face, trunk, and proximal upper and lower extremities [Figure 1a and b]. Systemic examination revealed no organomegaly or lymphadenopathy. Investigations revealed Hb of 9.4 g/dL, total count of 12.7 × 10^9/L, with neutrophils 44%, lymphocyte 22%, monocytes 9%, eosinophils of 25%, and absolute eosinophil count of 3.17 × 10^9/L. Liver function tests revealed elevated liver enzymes, serum glutamic-oxaloacetic transaminase of 66 IU/L and serum glutamic pyruvic transaminase of 142 IU/L, and alkaline phosphatase of 160 IU/L. Renal function tests and urinalysis were normal, while antinuclear antibodies and serology for hepatitis B, C, and HIV were negative. Skin biopsy revealed epidermal hyperkeratosis, follicular plugging, mild acanthosis, spongiosis, with a dense perivasculat inflammatory infiltrate in dermis composed of lymphocytes, histiocytes, and few eosinophils. [Figure 2a and b]. DRESS induced by imatinib was considered. The diagnosis was supported by a RegiSCAR score of 6 (Definite), and “probable” causality of imatinib based on the Naranjo probability assessment [Tables 1 and 2]. Imatinib was stopped and he was initiated on low-dose prednisolone at 0.5 mg/kg once a day. It was continued for a period of 3 weeks and tapered at a rate of 10 mg once a week after monitoring eosinophil counts and skin rash. After reaching a dose of 5 mg once a day, it was continued for another 3 months [Figure 3].

As the patient had complete resolution of skin rash, eosinophilia, and normalization of liver enzymes with steroids, imatinib rechallenge was considered. There were two reasons behind this decision. First, imatinib is a very effective drug for CML, associated with long-term survival of more than 90%, and all attempts must be made to try and utilize this drug as much as possible. Second, the costs of generic second line TKIs (nilotinib and dasatinib) are approximately 2–3 times that of imatinib and have significant implications for lifelong therapy. After a detailed discussion, imatinib was restarted at a lower dose of 200 mg/day under cover of prednisolone 5 mg once a day.

As per rechallenge ethics, imatinib was restarted at a lower dose of 200 mg per day, after 4 weeks upon resolution of the symptoms, but it resulted in recurrence of rash and eosinophilia after a period of 5 days. The severity of rash was similar to the original presentation. Rechallenge was attempted after admitting the patient, since imatinib is the
first drug for CML, cheap, and needs to be given life-long. However, he developed recurrent rash and eosinophilia after 2 weeks, indicating a positive rechallenge. As the patient was already on tapering dose of prednisolone, its dose was increased back to 0.5 mg/kg/day on reappearance of the rash. Imatinib was stopped and the patient was subsequently switched to dasatinib, at a dose of 100 mg per day, after 2 weeks, upon clearance of the rash. Dasatinib resulted in mild eruption of papulopustular acneiform lesions on forehead and neck. The same was controlled with topical steroids, which were discontinued after 2 weeks. He continues to be well 4 months after initiation of dasatinib and has achieved an optimal molecular response as directed by the European LeukemiaNet guidelines for CML.

**Discussion**

DRESS falls under the category of severe cutaneous adverse reactions, a category which includes Steven–Johnson’s syndrome (SJS) and acute generalized exanthematous pustulosis. This separate category highlights the clinical importance of identifying these drug reactions as they have significant systemic manifestations and can occasionally be life threatening or associated with long-term sequelae.
Table 3: Previous case reports of imatinib-induced DRESS

| S. no/Ref | Age/sex | Underlying disease | Latent period | Cutaneous lesions | Systemic symptoms | Investigations | Skin biopsy | Treatment and outcome | Rechallenge with Imatinib |
|-----------|---------|-------------------|---------------|-------------------|-------------------|---------------|-------------|-----------------------|--------------------------|
| 1[4]      | 78/F    | CML               | 7 wks         | Generalized MP rash | Fever LAP         | Eosinophilia | Blood culture- staph aureus | Imatinib stopped. | Not done |
| 2[5]      | 77/F    | CML               | 19 days       | Generalized polymorphous rash, oral erosions, facial edema | LAP | Eosinophilia | S/o drug-induced rash | Imatinib stopped, responded in 2 weeks. | Reintroduced after 3 months; rash and fever developed after 12 h of re-introduction. |
| 3[6]      | 53/F    | CML               | 18 days       | Macular rash over face and back, periorbital edema | Eosinophilia | | | Imatinib stopped prednisolone (1 mg/kg) started, improved in 8 days | After 2 weeks low-dose imatinib restarted lead to periorbital edema and eosinophilia in 2 weeks, stopped and restarted after 2 weeks with Prednisolone 5 mg |
| 4[7]      | 37/F    | CML               | 4 wks         | Generalized papular nonitchy eruptions | Fever, back pain | Eosinophilia | | Imatinib stopped but worsening was there | Reintroduction lead to oral erosions, fever, edema, and vomiting; shifted to dasatinib which lead to thrombocytopenia and intraabdominal bleeding |
| 5[8]      | 53/F    | CML               | 19 days       | Generalized rash, oral erosions, facial edema | Fever LAP | Leukocytosis, eosinophilia, increased CPK, urea, creatinine | | Imatinib stopped. Antihistaminics and topical steroids given, resolved in 2 weeks | |
| 6[9]      | 56/M    | CML               | 15 wks        | Generalized MP rash | Fever, muscle pain, B/L inguinal LAP | Eosinophilia | | Imatinib stopped. Dasatinib given. Improved after 1 month | |
| 7[10]     | 44/M    | DFSP              | 7 wks         | Rash over B/L ULs and LLs, yellow dry exudates over extensors, swelling over face, arms, and legs and oral erosions | B/L inguinal LAP | Eosinophilia, Increased SGOT | | Imatinib stopped, resolved after 2 weeks | Imatinib started at low dose after a month lead to eosinophilia, stopped and reintroduced at 50 mg dose with tapering dose of steroids |
| 8[11]     | 46/F    | GIST              | 2 wks         | Skin rash | Eosinophilia, increasing liver enzyme levels | | | Imatinib stopped | |

Contd...
Our patient demonstrated significant systemic symptoms which resolved rapidly with discontinuation of imatinib and addition of low-dose steroids.

DRESS occurring as a result of imatinib is rare, and only eight cases have been reported in literature so far. [12] Among these patients, six were diagnosed to have CML and one patient each had dermatofibrosarcoma protuberans and gastrointestinal stromal tumor. The median age of these patients ranged from 37 to 78 years, with characteristic symptoms appearing after a latent period of 14–49 days. This is consistent with descriptions of DRESS with other drugs, and similar to the timeline noted in our patient, with fever occurring after 10 days and skin rash after 25 days of starting imatinib.

The characteristic features of DRESS following imatinib include maculopapular rash, facial edema, lymphadenopathy, and eosinophilia. Our patient demonstrated all these features except lymphadenopathy.

Several clinical features associated with DRESS are nonspecific and may mimic those of other skin reactions, especially SJS. The RegiSCAR registry provides diagnostic criteria for DRESS which also allow differentiation from other skin reactions. Our patient had a score of 6 on this criteria, indicating definite DRESS.

Skin biopsy provides additional diagnostic support for the presence of DRESS and is characterized by a perivascular inflammatory infiltrate, acanthosis, and spongiosis. In the cases reported above, skin biopsy was available for an additional two patients, which showed similar findings to our case. [15,16]

Additional diagnostic support is lent by the presence of viral reactivation, notably HHV-6, which shows rising titers which parallel the development of symptoms. We performed testing only for HIV/HBV and HCV, which was negative.

The treatment of DRESS includes immediate discontinuation of the offending agent, with or without addition of corticosteroids. A clinical scoring system is available to classify patients into mild, moderate, or severe disease to enable early initiation of steroids for patients with severe disease. [15] Drug discontinuation usually leads to symptomatic improvement over a course of a few days to weeks.

In the patients described above, imatinib was withdrawn in all patients, and reintroduced in four. [15,16] However, rechallenge led to universal recurrence of rash and eosinophilia in all patients. In patient nos 5 and 7, the authors reported that low-dose imatinib was tolerated, along with a low dose of corticosteroids. [15,16] Patient 4 was not able to tolerate imatinib again and was started on dasatinib but that lead to mortality due to an unrelated cause. [7] Our patient tolerated dasatinib well, except for the development of a few acneform lesions, which were controlled with topicals.

Despite the recurrence of rash noted with all patients in literature, imatinib rechallenge with careful monitoring is a valid option in our setting. Imatinib is an excellent drug for CML associated with long-term survival exceeding 90% and is now affordable to the majority of the population. Second line TKIs are associated with a much higher lifetime cost compared to imatinib, and a high threshold must be kept before changing imatinib as first line therapy.

A clinical scoring system has been developed which allows scoring patients into mild, moderate, or severe disease, allowing close monitoring and early introduction of systemic steroids. [12] There are no randomized trials of treatment modalities, and treatment and steroid dosage should be adjusted according to severity of symptoms. [12] Steroids once started should be tapered off slowly over 6–8 weeks to prevent rebound disease manifestations. We continued steroids at a low dose of 5 mg/day for approximately 3 months, during which disease manifestations were kept under control.

Treatment guidelines for CML have been updated in 2020 and indicate that the treatment of CML can either begin with a first-generation TKI (imatinib) or a second-generation TKI (nilotinib or dasatinib). [15] Significant intolerance or adverse effects with imatinib warrant changing to a second line agent, which has a high likelihood of achieving clinical benefit.

To summarize, our patient demonstrates a rare occurrence of DRESS with imatinib, and to the best of our knowledge, it is the eighth case ever reported. For any patient presenting with rash and eosinophilia, any new drug should be discontinued, and low-dose steroids started. A rechallenge with a lower dose is reasonable, failing which an alternate drug should be started. It is essential to note that a relatively high threshold should be

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**Table 3: Contd...**

| S. no/Ref | Age/sex | Underlying disease | Latent period | Cutaneous lesions | Systemic symptoms | Investigations | Skin biopsy | Treatment and outcome | Rechallenge with Imatinib |
|----------|---------|--------------------|---------------|------------------|------------------|---------------|-------------|-----------------------|--------------------------|
| Current case | 55/M | CML | 6 wks | Generalized MP rash | Fever anorexia | Eosinophilia, transaminitis | Perivascular inflammatory infiltrate, acanthosis, spongiosis, intraepidermal vesicles | Imatinib stopped, resolve after 4 weeks | Imatinib reintroduced at a low dose, resulted in development of fever, skin rash, and eosinophilia |

CML – Chronic myelogenous leukemia, LAP – Lymphadenopathy, DFSP – Dermatofibrosarcoma protuberans, GIST – Gastrointestinal stromal tumor, B/L – Bilateral, UL – Upper limbs, LL – Lower limbs, SGOT – Serum glutamic-oxaloacetic transaminase, SGPT – Serum glutamic pyruvic transaminase, ARF – Acute renal failure, CPK – Creatine phosphokinase

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kept for changing therapy for CML, as it leads to unnecessary abandonment of a highly effective first line therapy.

**Declaration of patient consent**
The authors certify that appropriate patient consent was obtained.

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**Conflicts of interest**
There are no conflicts of interest.

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