

Multiple Drug Induced Hypersensitivity Syndrome Reactions in a Patient with Drugs that Have Known HLA Associations for Reactions

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Abstract

We report a rare case of a patient with chronic myeloid leukaemia (CML) who had severe drug hypersensitivity reactions with not only allopurinol and imatinib therapies for the CML, but also to a non-steroidal anti-inflammatory drug and an antibiotic. Each of the drugs (allopurinol and imatinib) when used alone, and in combination, had caused various combinations of fever (hyperpyrexia), rash and/or generalized edema. The patient had the HLA-B*58 haplotype that is associated with allopurinol induced Steven-Johnson syndrome. However, in our case, imatinib alone also caused a similar reaction. We discuss the other 'at-risk' HLA alleles and known drug reactions and that our patient was unfortunate to have all of these HLA alleles. Further studies are required to confirm whether the HLA-B*58 haplotype is a risk factor for imatinib induced adverse cutaneous drug reactions.

Keywords: Drug hypersensitivity; Imatinib; Allopurinol; HLA

Introduction

Chronic myeloid leukemia (CML) is considered to be the prototype of the myeloproliferative syndromes. It results from a balanced translocation between chromosomes 9 and 22 [t(9;22) the Philadelphia chromosome] creating a unique gene designated *BCR-ABL*, which codes a 210-kDa protein (p210) that functions as a constitutively active tyrosine kinase [1]. Imatinib (Glivec or Gleevec [US], Novartis) blocks tyrosine kinase activity and this therapy has revolutionized not only the treatment of CML, but also of *c-KIT* D816V mastocytosis, hypereosinophilic syndromes and gastrointestinal stromal tumours where excessive tyrosine kinase signaling leads to the malignancies [2].

However targeted the therapy may be, biologics are not without side effects and Type B (idiosyncratic or 'off target') reactions are possibly the most difficult of them that may necessitate stopping therapy [3].

Case Description

A 37-year-old female presented with weakness, low grade pyrexia and abdominal distension of 3 weeks duration. On examination, she had pallor and significant splenomegaly. Blood count showed Hb 8.6 g/dl, white cell count 300,000/mm³ and platelet count 1,12,000/mm³. Bone marrow confirmed the presence of BCR-ABL hybrid transcript with genomic breakpoint e13a2 corresponding to p210 consistent with CML. She was started on allopurinol 300 mg and imatinib 400 mg once daily. 10 days into treatment she had an episode of malena that settled spontaneously. Four weeks after allopurinol and imatinib, she developed high-grade fever, back pain and generalized tiny papular non-itchy eruptions. Imatinib was discontinued but the rash worsened developing into maculo-papular with periorbital edema. Allopurinol was stopped and a course of oral steroids and antihistamine prescribed. A week later the rash (Figure 1a) worsened with glossitis, hyperpyrexia (temperature up to 105°F), difficulty in swallowing and inflamed oral mucosa (Figure 1b). Eosinophilia was observed (baseline absolute eosinophil count was 14×10⁹/L that increased to maximum 33×10⁹/L). There was no source of infection with a normal chest X-Ray and a negative Mantoux test, negative for malaria, typhoid and dengue. Liver function test and renal functions at this stage were normal. It was thought to be DRESS (drug rash, eosinophilia, systemic symptoms) or drug induced hypersensitivity syndrome (DIHS) where inflammatory cytokines lead to fever following drug reaction.

Paracetamol and a single dose of aceclofenac (non steroidal anti-



Figure 1: a) Fine maculopapular rash. b) Inflamed oral mucosa

inflammatory drug, NSAID) use led to acute renal failure that was managed conservatively with fluids. All medications were stopped at this stage and finally by day 24 her symptoms resolved with normal renal function.

She was managed on hydroxycarbamide and discussed for a plan to restart on low dose imatinib. At home, the patient inadvertently took allopurinol instead of pantoprazole and developed a faint rash with generalized edema that fortunately settled in a few days. A re-challenge with imatinib led to recurrence of edema, hyperpyrexia, vomiting and mouth ulcers.

Delay in treatment due to these drug reactions led to myeloid blast crisis. Clavam (Amoxicillin, Clavulanic acid) was started for a respiratory infection but she was unable to tolerate this due to severe vomiting. After several discussions regarding available treatment options, she was started on an alternate tyrosine kinase inhibitor, dasatinib, which she fortunately tolerated quite well for about 2 weeks. However, severe thrombocytopenia led to profuse intra-abdominal

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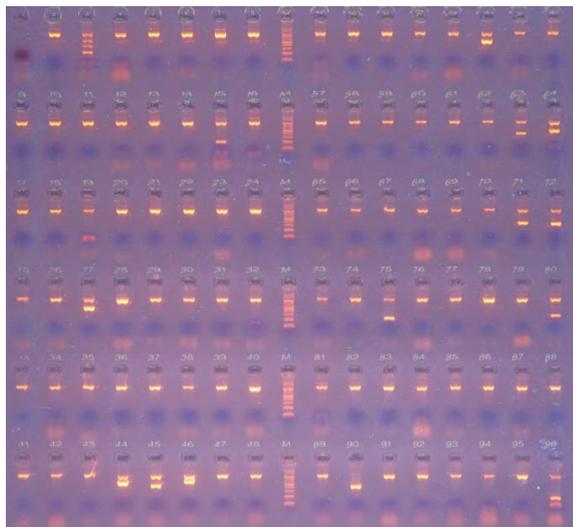


Figure 2: HLAABDR typing gel (well no 1, contamination control; well nos 2-24 pre-coated primers for HLA-A alleles; well nos 25-72 pre-coated primers for HLA-B alleles and well nos 73-96 correspond to pre-coated primers for HLA-DR alleles) with internal control (IC) band for all wells at 1070bp. The HLA type of the patient was HLA-A*02, A*02; HLA-B*40, B*58; HLA-DR*07, DR*15 with HLA-DRB4 and HLA-DRB5.

bleeding and she could not be resuscitated at another private hospital.

HLA ABDR sequence specific primer typing was done via low resolution PCR from DNA extracted from 200 µL EDTA whole blood by spin protocol using QiaAMP DNA Mini kit 50 (Qiagen), using the ABDR Histotype kit (BAG Health Care GmbH, Germany). The patient was found to be HLA-B*58 positive with lane corresponding to primer extending for HLA-B*58:01 (gel picture interpreted with HLA haplotype, Figure 2). The HLA type of the patient was:

HLA-A*02, HLA-A*02; HLA-B*40, HLA-B*58, HLA-DR*07, HLA-DR*15 and positive for HLA-DRB4 and HLA-DRB5

Discussion

Our patient had multiple drug hypersensitivity syndrome (MDHS) like reactions to several drugs, almost all of which have known HLA associations. There are two subtypes of MDHS, as suggested by Pichler and colleagues where one develops against different drugs given simultaneously (first subtype), and the second subtype in which the sensitisations develop sequentially, sometimes years apart [4-9]. One would consider that our patient belongs to the first subtype, but the subsequent 'sensitizations' to unrelated drugs also indicates that the second subtype is present (i.e., mixed phenotype). She not only initially reacted to allopurinol and imatinib but subsequently also to a NSAID and penicillin group of drugs. Whilst the HLA association is highest for allopurinol-induced reactions [10], the association with NSAID and penicillins is not that strong, and incidentally our patient had inherited the 'at-risk' HLA alleles that may have led to these severe reactions. Financial constraints prevented us from doing an exhaustive Specific IgE-based drug tests, regulatory T cell levels [5] or the Flow-assisted basophil activation assays.

This raises the moral/ethical question into whether clinicians should consider pre-testing selective patients for genetic variants to avoid unwarranted drug side effects. Two of these serious drug reactions is Stevens-Johnson syndrome/Toxic epidermal necrolysis (SJS/TEN) and Drug Rash, Eosinophilia and Systemic Symptoms (DRESS, or

also referred to as DIHS). The estimated occurrence of DRESS is between 1 in 1000 to 1 in 10,000 drug exposures [10,11]. Several commonly used drugs cause SJS or DRESS/DHS with the antiepileptic carbamazepine being the worst culprit, and not uncommonly lamotrigine, phenobarbital, sulfasalazine including allopurinol [12]. Our case fulfilled the major European (*RegiSCAR*, Kardaun 2007) and Japanese (Shiohara 2007) criteria for DRESS (Table 1). Allopurinol is widely used as concomitant therapy to prevent chemotherapy induced tumour lysis and hyperuricaemia. Studies have confirmed a strong and significant association between HLA-B*5801 and allopurinol induced severe skin reactions such as Steven Johnson syndrome or toxic epidermal necrolysis [12-14]. The HLA-B*58 haplotype frequency in Asian populations is estimated at 6%, and therefore it may be justified to screen for this haplotype if allopurinol is absolutely required. Other allopurinol-induced skin reactions such as hypersensitivity vasculitis, vesiculo bullous dermatitis, exfoliative dermatitis, pruritis, urticaria, lichen planus have been reported [14].

Up to 90% of patients experience skin rashes and a non-allergic periorbital edema with imatinib therapy [15]. Rashes are frequently pruritic and most commonly appear as erythematous, maculopapular lesions on forearms, trunk, and less frequently on the face. Hyperpyrexia, as seen in our patient, has been described in another report [16], including Steven Johnson syndrome with imatinib and allopurinol [17] and DRESS with imatinib [18,19]. Skin biopsies reveal the typical appearance of a toxic drug reaction with a mixed cellular infiltrate. Mild reactions (rash only) can be easily managed with antihistamines or topical steroids. Severe rashes with desquamative components (<1% of cases) are managed with immediate discontinuation of therapy and institution of systemic steroids (1 mg/kg/day). Imatinib can be started at 100 mg/ day, with dose increased by 100 mg/week while tapering the steroids, provided there is no recurrence of rash and no other treatment option exists other than imatinib. No reports exist until date on the HLA haplotype and risk of imatinib skin reactions. Although sensitivity to other tyrosine kinase inhibitors remains a possibility in these patients [20-25], our patient had no reaction for the two weeks on dasatinib suggesting (1) clinical cross reactivity to all tyrosine kinase inhibitors is not absolute; (2) the purported HLA-peptide presentation, if at all HLA-B*58:01 is for imatinib, is not same for all tyrosine kinase

Hospitalization
Reaction suspected to be drug-related
Acute rash*
Fever > 38°C*
Lymphadenopathy in at least two sites*
Involvement of at least one internal organ*
Blood count abnormalities (lymphopenia or lymphocytosis*, eosinophilia*, thrombocytopenia*)

a. RegiSCAR inclusion criteria 3 of the 4 starred criteria required for diagnosis

Maculopapular rash developing > 3 weeks after starting the suspected drug
Prolonged clinical symptoms 2 weeks after discontinuation of the suspected drug
Fever > 38°C
Liver abnormalities (ALT >100 U/L) or other organ involvement
Leukocyte abnormalities
Leukocytosis (>11 x 10 ⁹ /L)
Atypical lymphocytosis (>5%)
Lymphadenopathy
HHV-6 reactivation

b. Japanese consensus group criteria for DRESS/DIHS
Seven criteria required for diagnosis or first five for atypical DRESS

Table 1: DRESS/DIHS diagnostic criteria.

Drug	Reactions	HLA-B Allele	Population	References
Carbamazepine (anti-epileptic)	SJS/TEN Odds Ratio (OR) = 97.6	B*15:02	Han Chinese, Thai, Malay, Indian	Hsiao YH, 2013 [26]; Ding, 2010 [27]; Tasseneeyakul, 2010 [28]; Wu XT, 2010 [29]
Allopurinol (uricosuric agent) [§]	SJS/TEN OR=85.36 DIHS/DRESS OR = 99.59	B*58:01	Han Chinese, Thai, Japanese, Malay	Goncalo M, 2013 [12]; Ding, 2010 [27]; Kaniwa, 2008 [30]
Abacavir (Anti-retroviral)	DIHS/DRESS	B*57:01	Caucasians	Martin, 2004 [31]; Mallal, 2008 [32]
Lamotrigine (anti-epileptic)	DIHS/DRESS	B*58:01	Caucasians	Kazeem, 2009 [33]
Flucloxacillin	Liver Toxicity	B*57:01	Caucasians	Kostenko, 2011 [34]
Oxicam (NSAID) [§]	SJS/TEN	A2, B*73	Caucasians	Roujeau, 1987 [35]; Lonjou, 2008 [36]
Sulphamethoxazole	SJS/TEN	A29, B*38, B12, DR7 [§]	Caucasians	Lonjou, 2008 [36]
Co-amoxiclav [§]	Hepatotoxicity OR=2.56	DRB1*15	Caucasians	Donaldson, 2010 [37]

Table 2: The known 'at-risk' HLA-B alleles [including the alleles in our patient ([§])] associated with severe adverse drug reactions.

inhibitor group of drugs and (3) patients should be offered an alternative drug even though MDHS/DIHS was an issue with the alternative drug falling under the same category or generic version of the drug.

Our patient had inherited several 'at-risk' HLA alleles for severe drug reactions (Table 2 outlines the drugs and HLA alleles associated with DIHS), [26-37]. It is possible that herpes virus reactivation, most notably HHV-6, was the common underlying factor for the multiple drug reactions [38-42], although that was not proven in our case. We conclude that the HLA-B*58 haplotype may be a risk factor for drug hypersensitivity syndrome with imatinib therapy in patients who react to allopurinol, but this needs to be confirmed in further studies. Clinicians should be aware of the already identified 'high-risk HLA alleles' for adverse reactions to commonly used drugs, and how to counsel such patients.

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