ISSN NO. 2320-5407

Journal homepage: http://www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH

RESEARCH ARTICLE

IMATINIB CAUSING DRUG RASH WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS-A CASE REPORT.

Frederick Paswett, Bishurul Hafi. N.A., Romita Bachaspatimayum, Th. Bijayanti Devi.

Manuscript Info

Manuscript History:

Received: 14 January 2016
Final Accepted: 29 February 2016
Published Online: March 2016

Key words:
GIST, imatinib, DRESS.

Corresponding Author

Romita Bachaspatimayum

Abstract

Imatinib mesylate is a selective protein kinase inhibitor, currently used mainly for the treatment of malignancies like chronic myeloid leukemia (CML) and gastrointestinal stromal tumors (GISTs). The side-effect profile of this drug includes fluid retention, muscle cramps, diarrhoea, myelosuppression and skin rashes. Cutaneous toxicity has been reported in 18 to 69% of patients with GIST treated with doses ranging from 400 to 800mg once a day. Of these, maculo-papular eruptions and oedema developed most commonly. Herein we report a case of GIST who developed features of drug rash with eosinophilia and systemic symptoms (DRESS) on initiation of imatinib.

Introduction:-

Imatinib mesylate is a tyrosine kinase inhibitor approved for the treatment of CML and GISTs [1].The most common reported non-hematological side-effects include nausea, vomiting, abdominal pain, edema and weight gain [2]. All grades of cutaneous reactions have been reported in 18 to 69% of patients with GIST treated with a daily imatinib mesylate dose of 400 to 800 mg. Most commonly reported adverse effects are maculopapular eruptions, periorbital edema, and the less commoner ones include Stevens Johnson syndrome-Toxic epidermal necrolysis (SJS-TEN), acute generalized exanthematous pustulosis, hypopigmentation, lichenoid reaction, pityriasis rosea, and Sweet's syndrome [3].

Case Report:-

A 77 year old male post-operative case of GIST was started on Imatinib mesylate with a dose of 400mg once daily which was increased to 600mg once daily after 2 weeks. After 2-3 days he developed diffuse redness and swelling of face, more pronounced around the eyelids, which gradually progressed to dorsa of hands, ankles and shins. After 2-3 days he developed reddish skin rashes over the thighs, trunk, upper limb, scalp, palms and soles along with three bullous eruptions over the abdomen, ulcers at the sides of tongue with scaling and fissuring of lips. There was associated loss of appetite, weakness, insomnia , congestion of conjunctiva with mild watering and, cough and dyspnoea. There was no previous history of allergy or any recent history of taking any other drug.

He had attended Dermatology outpatient Department one month later. On examination, edema was present peri-orbitally [Figure 1] and over the hands and feet with generalised erythematous maculopapular rashes, including the oral cavity, palms and soles. Two bullae measuring 3cm x2cm and 2.5cm x 2cm and, an erosion, 1.5cmx1cm, were present over the anterior abdominal wall [Figure 2] .

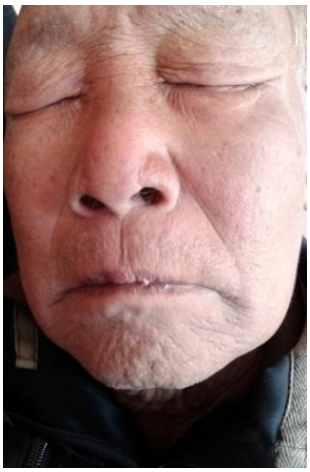


Figure 1. Peri-orbital edema

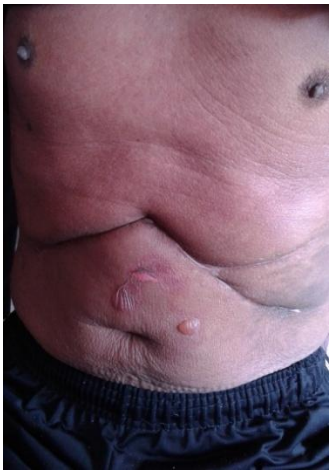


Figure 2. Erythematous maculopapular rash with bullae

Other systemic examinations were normal. Complete blood count showed a hemoglobin of 13.6 g/dl, total leucocyte count of 11.1× 10^3/µl , differential count of neutrophils-20%, lymphocytes-21%, monocytes-7% and eosinophils-52%, and blood smear showed leucocytosis with marked eosinophilia . The absolute eosinophil count (AEC) was 5.8 × 10^3/µl. Serum IgE was normal (131 IU/ml). Liver and renal function tests were normal. Histopathological examination of skin biopsy showed dermis with mild peri-capillary lymphocytic infiltration with a few scattered eosinophils[Figure 3].

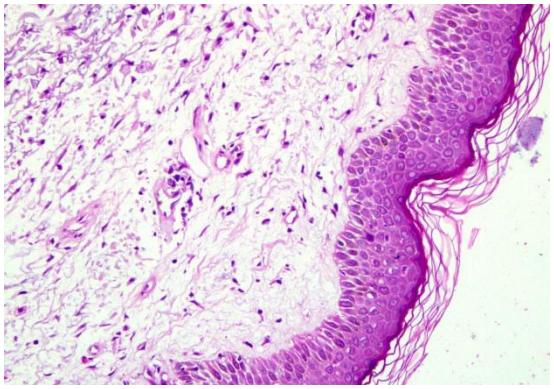
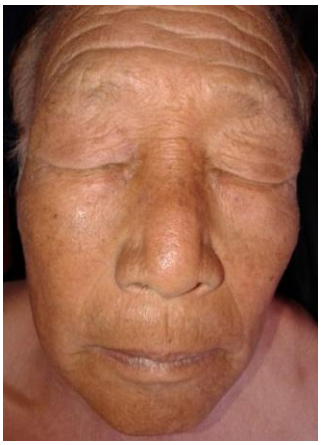


Figure 3. (H&EX100) mildly oedematous papillary dermis with mild pericapillary mixed inflammatory cell infiltration and scattered eosinophils.

Patient was started on oral prednisolone 20mg per day, which was gradually tapered, along with antihistamines with the advice to stop imatinib and switch over to another substitute as per the treating oncologist's advice. There was significant clinical improvement by 4 weeks [Figures 4&5] and eosinophil count returned to normal with AEC 0.2×10.^{3}



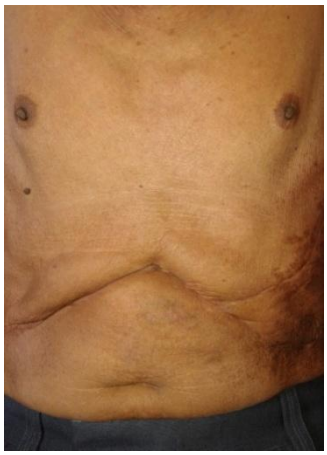


Figure 4. Reduced peri-orbital edema at 4 weeks

Figure 5. Resolution of lesions over the trunk.

Discussion:-

GIST is a malignancy thought to arise from interstitial cells of Cajal (ICC) and is the most common primary mesenchymal tumors of the gastrointestinal tract [4,5]. For many years, the mainstay of treatment for GIST is surgical resection.Imatinib mesylate and sunitinib maleate are competitive inhibitors of tyrosine kinases of bcr-abl, c-KIT and PDGFRA. Both drugs bind and stabilize the inactivated form of the receptor tyrosine kinases which leads to inhibition of phosphorylation and downstream KIT signaling activation [6]. The usual starting dose of Imatinib is 400 mg daily, but can be increased usually up to 800mg daily. A higher dose was also associated with a much higher rate of side effects which include edema, muscle cramps, nausea, vomiting, fatigue and rash. Hematologic effects include anemia, neutropenia, and elevated liver function tests [4]. Compared to CML patients, the incidence of skin reactions in GIST patients was in higher rate of occurrence as high as about 40-70% for patients receiving the higher dose (600-800mg daily). In our case also, within three days of increasing the dose to 600mg daily from 400 mg, he started developing the skin rash.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a severe adverse drug-induced reaction.The estimated incidence ranges from 1 in 1000 to 1 in 10,000 drug exposures [7]. The other noteworthy features are a delayed onset, usually 2-6 weeks after the initiation of drug therapy, and the possible persistence or aggravation of symptoms despite the discontinuation of the culprit drug [8]. The pathogenesis of DRESS syndrome is partially understood. Following mechanisms are suggested as possible pathophysiology : A)Reactive metabolite formation & genetic defects to metabolize it B)Intercurrent disease processs C)Viral reactivation, mainly HHV-6 D)Dynamic cytokine profile. F) The Pi-concept [9].

In an effort to define more accurately the DRESS syndrome, the RegiSCAR scoring system has been recently developed. RegiSCAR constitutes a European registry of severe cutaneous adverse reaction (SCAR), including Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and DRESS. In this line, Kardaun et al.modified the RegiSCAR's scoring system to grade DRESS cases as "no," "possible," "probable," or "definite" case [9].

The scoring system is shown in Table 1; skin rash suggestive of DRESS encompasses maculopapular rash and erythematous skin eruption, often progressing to exfoliative dermatitis associated with facial edema. Biopsy suggestive of DRESS is densely lymphocytic and eosinophilic infiltrated lesions with variable dermal edema. An absolute eosinophil count of more than 1.5 $x10^9$/L is toxic to endothelial cells and can lead to cardiac, gastrointestinal, central nervous system, pulmonary and renal dysfunction, including coronary artery thrombosis and eosinophilic pneumonitis [9]. According to the score system our case fall in to 'probable case' with final score 4.

Table 1 Scoring system for classifying DRESS cases as Definite, Probable, Possible, or No case, from Kardaun et al[9].

Score	-1	0	1	2
Fever>38°c	No/U	Yes		
Enlarged lymph nodes		No/U	Yes	
Eosinophilia		No/U	0.7-1.499x10^9L^{-1}	≥1.5 x10^9L^{-1}
Eosinophils				
Eosinophils if leukocytes<4.0 x 10^9L^{-1}			10-19.9%	>20%
Atypical lymphocytes		No/U	Yes	
Skin involvement				
Skin rash extent (%body surface area)		No/U	Yes	
Skin rash suggesting DRESS	No	U	Yes	
Biopsy suggesting DRESS	No	Yes/ U		
Organ involvement*				
Liver		No/U	Yes	
Kidney		No/U	Yes	
Muscle/ Heart		No/U	Yes	
Pancreas		No/U	Yes	
Other organ		No/U	Yes	
Resolution≥15days	No/U	Yes		
Evaluation of other potential causes				
Antinuclear antibody				
Blood culture				
Serology for HAV/HBV/HCV				
Chlamydia/mycoplasma				
If none positive and ≥3 of above negative			Yes	

DRESS=Drug reaction with eosinophilia and systemic symptoms; U= Unknown/Unclassifiable; HAV=hepatitis A virus; HBV=hepatitis B virus; HCV=hepatitis C virus.

*After exclusion of other explanations:1,one organ; 2, two or more organs. Final score < 2, no case; final score 2-3, possible case; final score 3-4, probable case; final score >5, definite case.

Conclusion:-

Cutaneous adverse drug reactions are very common with imatinib but the possibility of DRESS, though rare, should also be considered as it may cause serious complications. It can be treated with systemic steroids with a favourable outcome.

References:-

1. Savage DG and Antman KH. (2002): Imatinib mesylate – a new oral targeted therapy. N Engl J Med., 346: 683-93.
2. Baker DE. (2002) : Imatinib mesylate. Rev Gastroenterol Disord., 2(2):75-86.
3. Scheinfeld N. (2006): Imatinib mesylate and dermatology part 2 : A review of the cutaneous side effects of imatinib mesylate. J Drugs Dermatol., 5:228-31.
4. R. P. de Matteo, K. V. Ballman, C. R. Antonescu et al. (2009): "Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial".The Lancet., 373(9669):1097–1104.
5. J. A. Laurini and J. E. Carter. (2010):"Gastrointestinal stromal tumors: a review of the literature." Arch Pathol Lab Med.,134(1) :134–41.
6. A. W. Gramza, C. L. Corless, and M. C. Heinrich. (2009):"Resistance to tyrosine kinase inhibitors in gastrointestinal stromal tumors." Clin Cancer Res., 15(24)7510–18.
7. Fiszenson-Albala F, Auzerie V, Mahe E, et al. (2003): A 6-month prospective survey of cutaneous drug reactions in a hospital setting. Br J Dermatol.,149:1018-22.
8. Bocquet H, Bagot M, Roujeau JC. (1996): Drug-induced pseudolymphoma and drug hypersensitivity syndrome (Drug Rash with Eosinophilia and Systemic Symptoms: DRESS). SeminCutan Med Surg.,15:250-57.
9. Kardaun SH, Sidoroff A, Valeyrie-Allanore L, et al. (2007):Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? Br J Dermatol.,156:609-11.