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Case Report

Idiosyncratic adversity reported after oral consumption of an ayurvedic formulation containing bhallataka (*Semecarpus anacardium*): A case report

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ABSTRACT

Drugs associated adversities are common in health care practice. These adversities are often associated with the dose-related, time-related and methods of drug intake and their rationality in a given condition but can also be unrelated to either of these causes. Such unpredictable drug reactions are highly important from the perspective of safe use of a drug and to prevent complications from any such adversity which is relatively uncommon. The case reported here is a likely case of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) like idiosyncratic adversity after oral consumption of an ayurvedic formulation containing Bhallataka (*Semecarpus anacardium*). DRESS is found associated with many other classes of drugs but its association with ayurvedic drug has not yet been reported. Upon Naranjo probability scale the event scored 6, putting it into the category of probable drug related adversity. This report widens our understanding towards the possibility of delayed and idiosyncratic drug adversities upon the consumption of certain ayurvedic drugs.

1. Introduction

Common people reiterate Ayurvedic interventions to be safe. This safety assumption is among one important reason rendered by the people opting ayurvedic health care as their preferred health care provider in a given condition [1]. Safety of ayurvedic drugs however has occasionally been challenged and therefore the cases related to adversity associated with ayurvedic drugs are available in published literature. One very significant observation related to the adversity reporting of ayurvedic drugs is that barring a few [2,3] such adversity reports are almost negligibly reported by ayurvedic scholars. Most of the adversity reports associated with ayurvedic drugs available as the published literature are reported by the practitioners from secondary or tertiary health care settings.

There had always been a tussle between ayurvedic and allopathic practitioners regarding their claims of advantages and safety of one system over the other. Heavy metals and minerals and idiosyncratic adversities related to inadvertent use of ayurvedic drugs are often held responsible categorically for drug induced adversities [4,5], ayurvedic scholars on account of the shodhana process (purification techniques) employed in making of ayurvedic drugs, seem confident of safety of their formulations irrespective of the ingredients and account the inappropriate use of drugs as the main incriminating factor for any adversity related to Ayurveda drugs [6,7].

A few concerned scholars from Ayurveda and modern medicine however have brought their concern to bring equity in quality standards of all kind of medicines irrespective of their source of origin. For that reason, there is growing consensus in the Ayurveda sector itself for correcting the issues related to the quality of ayurvedic drugs [8,9].

Possibility of drug related adversity still remains even if the drugs are consumed in appropriate dose and schedule. Such idiosyncratic reactions constitute a great concern in the field of drug development owing to their unpredictability and potential systemic harm [10]. Idiosyncratic drug reactions are different from adverse drug reactions largely on account of rarity and unpredictability of the event and graveness of former comparing to the later. This is however important to know about any such idiosyncratic

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possibilities related with any drug use no matter how rare it ought to be. Reporting of such events therefore enriches the science and prepares it beforehand in case of such eventuality. Ayurveda proposes such events to be called as *vichitra prayarabdha* (unpredictable on the basis of conventional cause and effect theory) and *vikriti vishama samaveta* (where outcomes are different than that of inputs and hence outputs are not predictable on the basis of inputs) type of reactions.

We detail here a case of idiosyncratic drug reaction induced by an ayurvedic formulation containing Bhallataka (*Semecarpus anacardium*). The case qualifies to be called as an idiosyncratic reaction because the same compound is regularly being used on large number of patients suffering with autoimmune connective tissue and musculoskeletal disorders without observation of any apparent adversity. Second important observation putting emphasis upon idiosyncrasy of the given compound is the delayed onset of adversity and delayed normalization of symptoms upon withdrawal of incriminated drug.

2. Case report

A 21 year male diagnosed as a case of axial spondyloarthritis-Ankylosing Spondylitis (Ax-SpA-AS) on the basis of his clinical features, MRI of Sacroiliac joint and positive HLA-B 27 test (Table 1) came to Ayurveda- Arthritis Treatment and Advanced Research Center (A-ATARC), State Ayurvedic College and Hospital, Lucknow on 2 March 2022. He was examined clinically from Ayurveda perspectives and was diagnosed axial - amavata on the basis of prevailing symptoms. He was prescribed classical ayurvedic management of axial -amavata as is commonly prescribed at A-ATARC in such cases (Table 2). He responded well to the therapy in next 6 days (till 8 March 2022) as his pain and stiffness got reduced and he started feeling better. He continued same medicines on the advice of treating physician but from 8th day of continued treatment he started feeling of increased pain and stiffness. It went on like this for another 3–4 days and from 16 th March 2022 he started developing tiny red rashes on the flexure surface of both forearms (Photo 1). It gradually transformed as papulo-vesicular itchy lesions on dorsum of hands and flexor aspect of forearms. There was no associated pain or burning at the rash area. There were no additional constitutional features like fever except that he had some difficulty in deglutition. On examination he revealed to have mild tender lymphadenopathy in the gullet region. The rashes were not related to any topical drug application nor had any history of photosensitivity. Lesions were most intense on photo exposed area but were also available at covered places with reduced intensity. There was no immediate past history of any viral infection. He immediately reported about the developing features to his treating physician and was recommended to stop all medications containing bhallataka (Amrit Bhallataka (AB) and Sanjeevani Bati (SB))in a presumption of it leading to the adversity. He was also advised to have some other ayurvedic medicines to deal with rashes. AB and SB were stopped from 17 March 2022. In next 4 days after stopping the medicine, rashes started disappearing and were completely disappeared in next 10 days. New rashes also stopped appearing after 4 days of discontinuation of the medication. Rashes disappeared with dry and dark post rash spots at the place of their primary appearance (Photo 2, Table 3. Time line). The patient resumed taking other ayurvedic medicines (apart from those containing bhallataka) subsequently and is doing well till his recent follow up (12.4.2022). There are no new rashes and the spots of old rashes started disappearing. Clinical status of the patient in terms of spinal stiffness and pain pertaining to his primary problem (AS) has also improved. On his latest follow up (10.08.2022) the patient self-reported ~ 70% improvements in his initial clinical symptoms.

3. Discussion

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) like idiosyncratic adversity is a distinct phenomenon marked by delayed onset of adversity following the incriminated drug [11]. It usually presents with mild to severe features like fever, eosinophilia, lymphadenopathy and rashes [12]. The pathogenesis of DRESS syndrome is not well understood however it is believed to be caused due to genetic deficiency of detoxifying enzymes leading to an accumulation of drug metabolites. These accumulated metabolites subsequently bind to cell macromolecules and induce secondary immunological phenomena [13]. The other possible cause is the genetic associations between human leukocyte antigens (HLA) with drug hypersensitivity. Some examples of this association are HLA-B*1502 associated carbamazepine (CBZ)-induced Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN); HLA-B*1508 and associated allopurinol induced SJS/TEN [14,15]. Although such drug hypersensitivity association involving *S. anacardium* compounds with HLA B27 has not yet been reported, there are strong plausibility of existence of such possibility based upon observations with other HLA drug hypersensitivity cases. At least in one study the occurrence of HLA-B27 in female patients with seropositive RA (especially in those with ANA), was found associated with an increased risk for drug-induced agranulocytosis [16].

Bhallataka (*S. anacardium*), the drug of concern in this case is a widely prescribed drug in Ayurvedic practice [17]. Bhallataka in particular is recommended as a first line drug in ama induced

Table 1
Relevant investigations and their findings.

No	Date	Name of investigation	Findings
1	2.2.2022	MRI Bilateral Sacro-iliac joints	Ill-defined areas of altered signal intensity appearing hypointense on T1W1, hyperintense on T2Wl as well as STIR seen involving right iliac and sacral bones surrounding the sacroiliac joints. Similar signal intensity smaller areas seen involving left iliac and sacral bones. Another ill-defined area appearing hyper intense on both T1 and T2WI showing suppression on STIR seen in left sacral bone on left side. No obvious joint effusion seen Pubic bones and ischium are normal IMPRESSION: 1. Acute right sided sacroiliitis 2. Acute on subacute/chronic left sided sacroilitis
2	2.2.2022	Hematology	Hb-13.0 gm% ESR-44mm
3	2.2.2022	Biochemistry	Serum Creatinine –1.00 mg/dl Serum ALT-18 IU/L
4	2.2.2022	Immunology-Serology	C Reactive Protein- 92.71 mg/dl
5	13.3.2022	HLA-B-27	Positive

Table 2
Recommended ayurvedic treatment.

Number	Name of the drug	Dose	Frequency	Any special precaution or instruction
1.	Dashmula quath	30 ml	Two times in a day	Prepare fresh every time
2	Tablet Amavatari Rasa	125 mg	Two times in a day	To be taken after food
3	Amrit Bhallataka Avaleh	2.5 gm	Two times in a day	To be taken after food preferably with milk
4	Tablet Sanjeevani Bati	125 mg	Two times in a day	To be taken after food

Photo 1. Images of disappearing rashes after withdrawal of the suspected drug (31.3.2022).

Photo 2. Images of pappulo-vesicular lesions probably resulting from oral intake of Bhallataka preparation (19.3. 2022).

pathologies including various autoimmune disorders having features of inflammatory arthritis. It is for this reason, bhallataka becomes the drug of choice in cases like RA and AS [18]. Bhallataka is usually available and clinically used in avaleha form (Bhallatakavaleha, Amrit Bhallataka) or as tablet form (Sanjeevani Bati) where bhaalataka is one of several ingredients in the compound formulation. Bhallataka Kshirapaka is also recommended for its use in RA [19].Recently Amrit Bhallataka was also used in

Table 3
Timeline of events occurring in the case.

Date	Important events
2.2.2022	MRI Sacroilliac Joints suggestive of Axial Spondylo-Arthritis Started treatment under the guidance of a qualified rheumatologist
2.3.2022	No response obtained from conventional treatment. Visited A-ATARC, at State Ayurvedic College, Lucknow
3.3.2022	Started recommended ayurvedic drugs
10.3.2022	Increased pain and stiffness
13.3.2022	HLA-B-27 Positive report
16.3.2022	Development of papulo-vesicular rashes on flexure aspect of both forearm and dorsal surface of both hands
17.3.2022	Sanjeevani Bati and Amrit Bhallataka stopped
21.3.2022	Rashes started disappearing
27.3.2022	Rashes completely disappeared with post rash residues
17.4.2022	Patient is symptomatically improved and doing well. Post rash residues almost disappeared
10.8.2022	Patient is symptomatically improved and stable with a self-report of 75% improvement in his initial symptoms.

treating a case of Covid-19 induced pneumonia with good responses [20]. Amrit bhallataka in a well-organized RCT also has demonstrated beneficial effects in osteoarthritis of knees [21].

Bhallataka is always recommended to be used with caution in ayurveda. For its properties of being ushna (hot) and tikshna (sharp), it is recommended to be used with caution in patients having pitta prakriti. This is not recommended during summer and should be used with extreme caution in people having hepatobilliary disorders, bleeding disorders, ulcer or GERD. Incidentally a RCT of a well standardized product of amrit bhallataka has reported liver enzymes elevation [21]. Commonest adversity reported with bhallataka in Ayurveda literature is burning sensation at prepuce, urinary and peri anal area. Upon occurrence of any such symptom, the drug is advised to be stopped immediately. The acute adversity with skin reactions are probably due to the phenolic compounds present in the pericarp of the bhallataka seeds Despite of being considered as a drug to be used carefully, in routine clinical practice of ayurvedic rheumatology where this drug is maximally utilized, such adversities are rarely observed. During 2021–2022 in one working year, about 500 cases of rheumatoid arthritis and Spondyloarthritis were seen in Ayurveda- Arthritis Treatment and Advanced Research Center (A-ATARC). Over 75% of these patients were recommended for Amrit Bhallataka and Sanjeevani Bati either alone or in combination. Usual period of recommendations of these drugs in such patients was found ~6 months. So far in any of such cases any adversity related to bhallataka use was not reported prior to the one which is reported through this case. Toxicity studies on bhallataka have previously been carried out and found no specific toxicity association with bhallataka [22,23]. Shodhana (purification) of bhallataka is said to play a crucial role in rendering safety to bhallataka [24]. Despite of this clinical safety, for its textual caution and potential of causing harm based upon limited published literature, bhallataka had been the first drug in the given case which could have been linked with reported adversity.

This case where oral use of bhallataka provoked a DRESS like idiosyncratic reaction in a HLA-B-27 patient is unique example of specific drug related adversities may be invoked by ayurvedic drugs. Using The Naranjo Algorithm, or Adverse Drug Reaction Probability Scale to assess whether there is a causal relationship between an identified untoward clinical event and a drug using a probability scores the case has scored 6 and therefore was a probable case of drug related adversity (coming under the score category between 5 and 8) [25]. Knowing about such reactions and reporting them adds to the existing knowledge by enriching the literature through precise documentation of the experiences and observations. Eventually, such knowledge prepares us for future in order to prevent or abort such complications at the earliest without leading to any damage to the recipient. Such reporting also invoke us to look into precise mechanisms of such occurrence. Since Bhallataka is already known for its potential of causing adversities, an analysis of its active compounds may give us clue about a particular component in the whole drug having adversity potential. Once identified, approaches can be made to isolate this principle by adopting some separation techniques. Reporting adversities, on any account do not mean to show the limitations of any system of medicine but rather is an approach to improve the acceptance of a given system by improving its safety. This case report of DRESS like idiosyncratic reaction upon oral consumption of a Bhallataka preparation is one step towards a greater acceptance of Ayurveda among masses with due concern about its safety.

4. Patient's perspective

I started medicines from 03 March 2022 and continued to take them for about 10 days. Then after I started developing small rashes on hands and foot along with itching. Also I had swelling and rashes at scrotal and penile area. It was oozing also. On the recommendation of my treating physician, I stopped all medicines. It remained stopped for about 8-10 days. The rashes and selling at penile area got cured in this time. The rashes on hands and feet also started disappearing but with occasional eruptions at some places. I started other Ayurvedic medicines and after 6-7 days I got completely cured.

5. Conclusion

Knowing about the drug related adversities are definitive ways of improving the health care delivery by observing a caution on selected drugs and getting prepared beforehand in case of an eventuality. Ayurvedic drugs are sometimes found to invoke drug related adversities. Such adversities may be because of inadvertent and unsupervised use of the drug or can also be idiosyncratic where despite of being prescribed and consumed in a stringent manner, adversities may occur. This report of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) like idiosyncratic adversity reported after oral consumption of ayurvedic formulations containing Bhallataka (*S. anacardium*) is highly important from the perspectives of finding a new mechanism of individualized drug interactions leading to adversities. HLA-B-27 association with the drug consumed and a genetic predisposition leading to accumulation of toxic metabolites causing the delayed onset of adversities are highly probable explanations of drug adversity in this case.

Credit statement

Sanjeev Rastogi: Conceptualization, writing, editing and approval.

Preeti Pandey: Writing, Review, Editing and approval.

Ethical aspects of the case report

Consent from the patient was obtained for publication of this adversity report in order to enrich the medical literature with newer information related to safety of ayurvedic drugs. Due care was taken for not revealing identity of the patient while putting his personal information, investigation reports and photographs in the submitted case report.

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Declaration of competing interest

None.

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References

[1] Rastogi S, Tiwari V, Jatav SP, Singh N, Verma S, Verma S, et al. A survey of patients visiting an Ayurvedic teaching hospital for factors influencing the decision to choose ayurveda as a health care provider. J Ayurveda Integr Med 2022 Jan 22:100539. https://doi.org/10.1016/j.jaim.2021.100539. Epub ahead of print. PMID: 35078695.

[2] Rastogi S. Urticarial rashes following guggulu intake: a case report. J Ayurveda Integr Med 2017 Jul-Sep;8(3):205–6. https://doi.org/10.1016/j.jaim.2017.04.004. Epub 2017 Aug 18. PMID: 28826837; PMCID: PMC5607394.

[3] Rastogi S, Singh RH. Ranjana Adverse effects of Ayurvedic drugs: an overview of causes and possibilities in reference to a case of Vatsanabha (Aconite) overdosing. Int J Risk Saf Med 2007;19(3):117–25.

[4] Karousatos CM, Lee JK, Braxton DR, Fong TL. Case series and review of Ayurvedic medication induced liver injury. BMC Complement Med Ther 2021;21(1):91. https://doi.org/10.1186/s12906-021-03251-z. PMID: 33714265; PMCID: PMC7956115.

[5] Vamadevaiah RM, Santhekadur PK. Herbal immunity booster-associated liver injury during COVID-19 pandemic and aflatoxins. J Clin Exp Hepatol 2022 Jan-Feb;12(1):252–3. https://doi.org/10.1016/j.jceh.2021.08.021. Epub 2021 Aug 26. PMID: 34462625; PMCID: PMC8388140.

[6] Ruknuddin G, Narayanam S, Nesari TM. Do tinospora cordifolia cause hepatic damage? J Clin Exp Hepatol 2022 Jan-Feb;12(1):244. https://doi.org/10.1016/j.jceh.2021.09.006. Epub 2022 Jan 12. PMID: 35068810; PMCID: PMC8766692.

[7] Rastogi S, Pandey DN. Herbal immune booster-induced liver injury in the COVID-19 pandemic - a cautious interpretation is desired before any generalization is attempted. J Clin Exp Hepatol 2022 Jan-Feb;12(1):256–7. https://doi.org/10.1016/j.jceh.2021.08.006. Epub 2021 Aug 14. PMID: 34413585; PMCID: PMC8364168.

[8] Rastogi S. Ayurveda formulations: a roadmap to address the safety concerns. J Ayurveda Integr Med 2018;9(1):81–2. https://doi.org/10.1016/j.jaim.2018.02.002.

[9] Rastogi S. Safety in Ayurveda: need to bring the house in order. Indian J Gastroenterol 2018 Jul;37(4):374–5. https://doi.org/10.1007/s12664-018-0883-4. Epub 2018 Aug 30. PMID: 30168072.

[10] Uetrecht J, Naisbitt DJ. Idiosyncratic adverse drug reactions: current concepts. Pharmacol Rev 2013;65(2):779–808. https://doi.org/10.1124/pr.113.007450. Published 2013 Mar 8.

[11] Choudhary S, McLeod M, Torchia D, Romanelli P. Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. J Clin Aesthet Dermatol 2013;6(6):31–7.

[12] De A, Rajagopalan M, Sarda A, Das S, Biswas P. Drug reaction with eosinophilia and systemic symptoms: an update and review of recent literature. Indian J Dermatol 2018;63:30–40.

[13] Choquet-Kastylevsky G, Intrator L, Chenal C, Bocquet H, Revuz J, Roujeau JC. Increased levels of interleukin 5 are associated with the generation of eosinophilia in drug-induced hypersensitivity syndrome. Br J Dermatol 1998;139(6):1026–32. https://doi.org/10.1046/j.1365-2133.1998.02559.x. PMID: 9990366.

[14] Chung WH, Hung SI, Hong HS, Hsih MS, Yang LC, Ho HC, et al. Medical genetics: a marker for Stevens-Johnson syndrome. Nature 2004;428(6982):486. https://doi.org/10.1038/428486a. PMID: 15057820.

[15] Hung SI, Chung WH, Liou LB, Chu CC, Lin M, Huang HP, et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. Proc Natl Acad Sci U S A 2005;102(11):4134–9. https://doi.org/10.1073/pnas.0409500102. Epub 2005 Mar 2. Erratum in: Proc Natl Acad Sci U S A. 2005 Apr 26;102(17):6237. PMID: 15743917; PMCID: PMC554812.

[16] Schmidt KL, Mueller-Eckhardt C, Breithaupt H. HLA-B27, antinuclear antibodies and drug-induced agranulocytosis. Klin Wochenschr 1978 Dec 1;56(23):1189–91. https://doi.org/10.1007/BF01476864. PMID: 309534.

[17] Semalty M, Semalty A, Badola A, Joshi GP, Rawat MS. Semecarpus anacardium Linn.: a review. Phcog Rev 2010;4(7):88–94. https://doi.org/10.4103/0973-7847.65328.

[18] Saraf MN, Ghooi RB, Patwardhan BK. Studies on the mechanism of action of Semecarpus anacardium in rheumatoid arthritis. J Ethnopharmacol 1989 Apr;25(2):159–64. https://doi.org/10.1016/0378-8741(89)90017-2. PMID: 2747250.

[19] Vinod N. Ade, role of bhallattaka kshira paka in the management of amavata (rheumatoid arthritis). Joinsysmed 2015;3(3):122–8.

[20] Rastogi S. Ayurveda co-interventions have supported complete recovery in severe COVID-19 infection with a chest severity score 18/25: a case report. J Ayurveda Integr Med 2022 Apr-Jun;13(2):100417. https://doi.org/10.1016/j.jaim.2021.02.008. Epub 2021 Mar 12. PMID: 33727768; PMCID: PMC7953452.

[21] Raut A, Bichile L, Chopra A, Patwardhan B, Vaidya A. Comparative study of amrutbhallataka and glucosamine sulphate in osteoarthritis: six months open label randomized controlled clinical trial. J Ayurveda Integr Med 2013;4:229–36.

[22] Murty GK. Clinical toxicity study of Semecarpus anacardium Linn. f. Indian J Exp Biol. 1974 Sep;12(5):444–6. PMID: 4448495.

[23] Patwardhan B, Saraf MN, David SB. Toxicity of semecarpus anacardium extract. Ancient Sci Life 1988;8(2):106–9.

[24] Sahu PK, Tiwari P. Impact of shodhana on Semecarpus anacardium nuts'. In: Akram M, editor. Alternative medicine - update. London: IntechOpen; 2020. https://doi.org/10.5772/intechopen.94189.

[25] Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharacol Ther 1981;30:239–45.