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HERBAL-INDUCED APLASTIC ANAEMIA SECONDARY TO FERULA ASAFOETIDA IN TWO PAEDIATRIC PATIENTS: CASE SERIES.

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ABSTRACT

Aplastic anaemia is a rare and heterogeneous disorder. It is defined as pancytopenia with a hypocellular bone marrow in the absence of an abnormal infiltrate or marrow fibrosis.[1] We, hereby, describe a newly observed genuine relationship between herbal ingestion of *Ferula Asafoetida* (*Heltit*) and a resultant depressed marrow in conjunction with deranged liver enzymes observed in 8-year-old and 9-year-old patients respectively.

KEYWORDS: *Ferula Asafoetida, Paediatric, Aplastic Anaemia, Heltit, Saudi Arabia.*

List of Abbreviations	
IgM	Immunoglobulin M
IgG	Immunoglobulin G
WBC	White Blood Cells
ANC	Absolute Neutrophils Count
ESR	Erythrocyte Sedimentation Rate
CRP	C – Reactive Protein
LDH	Lactic Acid Dehydrogenase
ALT	Alanine Transaminase
AST	Aspartate Transaminase
GGT	Gamma-GlutamylTranferase
CMV	CytoMegaloVirus
ANA	AntiNuclear Antibody
ASCA	Anti-Saccharomyces Cerevisiae Antibodies
ASMA	Anti-Smooth Muscle Antibody
GPA	Anti-Granulomatisis with Polyangiitis
NPA	Naso-Pharyngeal Aspirates
LKM	Anti-Liver-Kidney Antibody
HLH	Hemophagocytic LymphoHistiocytosis
CSA	CycoloSporin A

INTRODUCTION

Haematopoietic failure of the marrow with attendant scanty or absent cellular precursors describes the aplastic bone marrow.[2,3] The male-to-female ratio is approximately 1:1. Although aplastic anemia occurs in all age groups, a small peak in the incidence is observed in childhood.[4,5] Such an injury to bone marrow occurs in a multitude of settings. Examples include, but not limited to, idiopathic (Accounts to mostly 65%), autoimmune, infectious, drug-induced, chemical-related and hereditary etiologies.[6,7]

On the other end of the spectrum, herbs have always been a constant source of medicines, that people used to medicate their ill. *Ferula asafoetida* is herbaceous plant of the umbelliferae family. It is oleo gum resin obtained from the rhizome and roots of plants. This spice is used as a digestive aid, in food as a condiment and in pickles. It is used in modern herbalism in the treatment of hysteria, some nervous conditions, bronchitis, asthma and whooping cough.[8]

So far, we have caught sight of a succession between Aplastic anaemia and *Ferula Asafoetida* (*Heltit*) consumption noted and became clinically and biochemically evident following this herbal ingestion in two children aged 8 and 9 years correspondingly.

CASE (1) *September / 2020*
An 8-year-old female, who is previously healthy. She started experiencing jaundice 20 days associated with generalized bruises 5 days prior to her presentation to the Emergency department.

She was in her usual state of health until 20 days ago, when the mother noticed her daughter having yellowish skin and eyes, with fatigability and anorexia. Besides, she had diarrhea and occasional vomiting simultaneously with the jaundice. Her urine color was dark, whilst no change in stool color was noted. Therefore, she sought medical attention in a periphery hospital where an assumptive diagnosis of hepatitis A was placed, even though she was fully vaccinated!! It is worth noting that her full blood count that time was totally normal, her hepatitis A IgM was negative, while IgG was positive, apparently due to the vaccine previously received.

As no improvement was perceived, the mother sought herbal remedy, and gave her *Ferula Asafoetida* (*Heltit*), one big spoon in a gallon of water, which she drank over 5 days, during which she had worsening jaundice and developed bruising all over her limbs, face, and back.

She went to a secondary care center in Riyadh, where she was found to have pancytopenia, with evident gum bleeding, so platelets transfusion was commenced and was thoroughly investigated, which revealed no obvious cause! Hence, she was referred to our center for Bone Marrow Aspiration (BMA).

Upon encountering her at our institution, history of lumps, trauma, fever at the time of interview or prior to, or the same presentation in the family were all denied. Apart from the above-mentioned bruising, she did not have any rash. Additionally, there was no family history of any liver diseases, blood disorders or malignancies. Upon examination, she was icteric, had bruising over limbs and face, and petechial rash in the mouth. The patient was afebrile, with no evident abnormalities revealed upon her general, chest, cardiovascular and abdominal examinations. Labs and imaging were as follow (Table 1):

Table 1: Labs and imaging studies of case. [1]

Labs/Imaging / **Date**	**Admission day**	**Present day**	**Reference Range**
WBC	2.3 *10e9/L*	1.12 *10e9/L*	4.3 -11.3 *10e9/L*
ANC	0.24 *10e9/L*	0.01 *10e9/L*	1.35 – 7.5 *10e9/L*
Hemoglobin	7.8 *g/dl*	9.4 *g/dl*	11-15 *g/dl*
Platelets	17 *10e9/L*	37 *10e9/L*	155 - 435*10e9/L*
Reticulocytes	0.30 *%*	0.14 *%*	0.5 - 1.5 *%*
ESR	2 *mm/H*	2 *mm/H*	0 – 20 *mm/H*
CRP	12.4 *mg/L*	21.3 *mg/L*	1 – 3 *mg/L*
LDH	351 *U/L*	367 *U/L*	125 – 220 *U/L*
Ferritin	801 *ng/ml*	___	10 -204 *ng/ml*
Fibrinogen	1.78 *g/L*	2.54 *g/L*	1.61 – 4.39 *g/L*
ALT	1035 *U/L*	42 *U/L*	0 – 55 *U/L*
AST	175 *U/L*	26 *U/L*	5 – 34 *U/L*
GGT	71 *U/L*	66 *U/L*	9 – 36 *U/L*
Total Bilirubin	65.9 *umol/L*	9.4 *umol/L*	3 -20 *umol/L*
Direct Bilirubin	47 *umol/L*	5.8 *umol/L*	0 -8.6 *umol/L*
Uric Acid	151 *umol/L*	171 *umol/L*	150 – 350 *umol/L*
Hepatitis A IgM	Negative		
Hepatitis A IgG	Positive		
CMV, EBV, Parvovirus B19	Negative		
ANA, ASCA, ANCA, ASMA, GPA	Negative		
Hepatitis B, C	Negative		
Brucella, NPA	Negative		
Stool for Schistosoma, Adenovirus and Rotavirus	Negative		
Coagulation Profile	Normal		
BMA	Hypocelluar bone marrow (Cellularity 10%), shows decreased trilineage hematopoiesis.		
Chromosomal analysis of the bone marrow	Normal		

The patient was then managed with multiple blood products transfusion and eltrombopag, her liver enzymes were spontaneously normalized, but she was left with bone marrow failure for transplantation therapy. Moreover, while hospitalized, the mother gave her steeped Safran in water, apparently without medical consultation. Consequently, few hours later, the patient unfortunately developed a generalized exanthem that is showed in the pictures below, but no other symptoms:

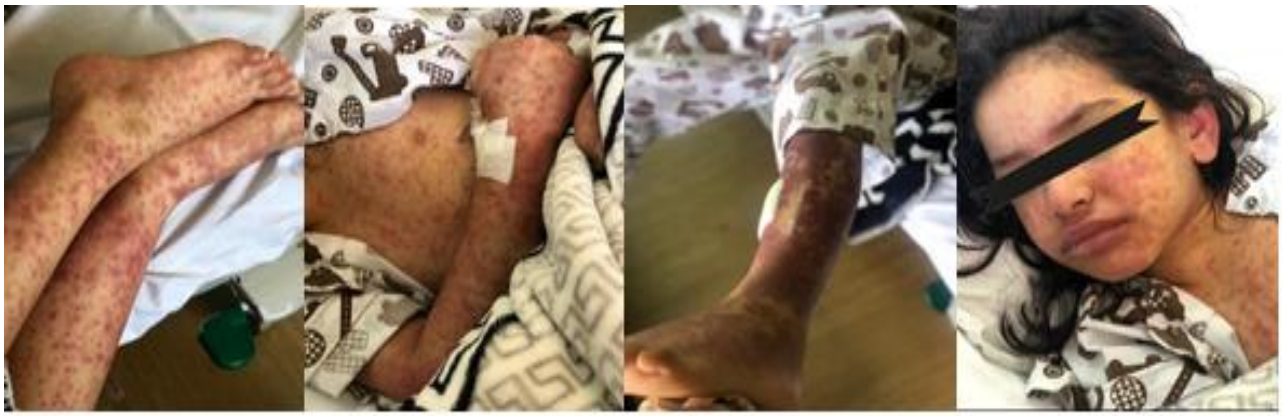

Figure (1): Pictures of the child's purpuric skin lesions.

Skin biopsy later proved the autoimmune chemical reaction as it histologically demonstrated ''Mild spongiosis with dyskeratotic keratinocytes and sparse upper dermal inflammation''.

CASE (2) ***July / 2012***

A 9-year-old boy, presented to our hospital when he was 4-years old with the complaint of easy bruising for 6 months, and yellowish discoloration of the skin and eyes for 4 months prior to his presentation. There was no history of fever, abdominal pain, Joints pain or skin rashes, nor weight loss. However, a significant history of herbal medication ingestion that consists of a mixture of: Asafoetida mainly, Myrrh, and Astragalus sarcocolla few weeks prior to his illness was denoted. No family history of similar illness or inherited hematological diseases. The patient was admitted twice before in secondary care centers, where work up was done including bone marrow biopsy. He received frequent packed red blood cells and platelets transfusions. Eventually, the parents landed in our hospital.

The physical examination revealed a vitally stable, normally grown child, who was deeply icteric, pale with multiple cautery marks on the abdomen and back, and hepatomegaly. The rest of examination was unremarkable. Investigations and imaging were as follow (Table 2):

Table (2): Labs and imaging studies of case.

Labs/Imaging / Date	Admission day	Present day	Reference Range
WBC	2.53 *10e9/L*	8.45 *10e9/L*	4.3 -11.3 *10e9/L*
ANC	0.9 *10e9/L*	3.25 *10e9/L*	1.35 – 7.5 *10e9/L*
Hemoglobin	5.2 *g/dl*	13.8 *g/dl*	11-15 *g/dl*
Platelets	5.8 *10e9/L*	199 *10e9/L*	155 - 435*10e9/L*
Reticulocytes	6.8 *%*	0.72 *%*	0.5 - 1.5 *%*
ESR	24 *mm/H*	___	0 – 20 *mm/H*
CRP	3.2 *mg/L*	___	1 – 3 *mg/L*
LDH	620 *U/L*	277 *U/L*	125 – 220 *U/L*
Ferritin	1627 *ug/L*	___	30 – 620 *ug/L*
Fibrinogen	3 *g/L*	___	1.61 – 4.39 *g/L*
ALT	2466 *U/L*	16 *U/L*	0 – 55 *U/L*
AST	2787 *U/L*	30 *U/L*	5 – 34 *U/L*
GGT	78 *U/L*	75 *U/L*	9 – 36 *U/L*
Total Bilirubin	364 *umol/L*	8 *umol/L*	3 -20 *umol/L*
Direct Bilirubin	355 *umol/L*	3 *umol/L*	0 -8.6 *umol/L*
Uric Acid	84 *umol/L*	128 *umol/L*	150 – 350 *umol/L*
Hepatitis A IgM	Negative		
Hepatitis A IgG	Positive		
CMV, EBV, Parvovirus B19	Negative		

ANA, ASCA, ANCA, ASMA, GPA, LKM	Negative
Hepatitis B, C	Negative
Brucella, Leishmania	Negative
Rheumatoid factor, Complement 3, 4	Normal
Coagulation Profile	Normal
Chromosomal analysis of the bone marrow	Normal
BMA	Severe hypocellular marrow (<10%) compatible with aplastic anemia. Marked hemophagocytosis with no HLH activity, profound hypocellularity, and megakaryocytopenia. No abnormal cells noticed.
Liver Biopsy	Minimal portal inflammation with endothelitis and minimal portal fibrosis. No viral cytopathic changes could be seen.
Abdominal Ultrasound	Enlarged liver measuring 14 cm with minimal free fluid and normal spleen.

Hospital course

The patient was admitted to the ward on July 12, 2012 as a case of cholestatic jaundice with high liver enzymes and pancytopenia for workup and diagnoses.

1) For Pancytopenia: Work up investigations were done to rule out virology causes, malignancy and storage diseases. He went for bone marrow biopsy on July 16, 2012 with no complications and biopsy was reported that there is a sever hypocellular marrow compatible with aplastic anemia. No abnormal cells were noticed. HLH was ruled out by the absence of the required diagnostic criteria. Liver biopsy was done with no complications, reported that there is minimal portal inflammation with endothelitis and minimal portal fibrosis but no viral cytopathic changes could be seen, and no HLH activity. Based on that he was labeled as a case of severe aplastic anemia with unclear etiology, and planned for bone marrow transplant. However, the patient showed dramatic improvement on immunosuppressants (CSA) which was started on Sep 2012, with maximum response on May 2014 (PLTs were the last to recover > 150 x 10.e9/L), and was transfusion free since Dec-2012. CSA was then slowly weaned off till 14-02-2015. No bone marrow transplant was needed.

2) For the liver: The patient showed spontaneous improvement in his liver function test with total normalization of the liver enzymes and bilirubin serum level on 17-10-2012.

DISCUSSION

Both of our reported cases have in common the succession of Asafoetida consumption, and the development of bone marrow suppression, represented as pancytopenia, with all the extensive work up to rule out other congenital, viral, autoimmune, storage, or malignant causes of bone marrow failure, which revealed no other apparent factor that could be accused.

We are left with the herbs effect, that might be even the trigger of the liver derangement in the second case, as the mother denied the herbs consumption prior to the liver insult in the first one.

There was a study on mice in the literature, published in 2015, which linked between the chronic use of Asafoetida, and the adverse effects on liver and blood parameters.[9] This could be very true in humans!

Even though Asafoetida is a popular and reputed herb in many cultures, due to its numerous benefits and soothing effects, it is immensely vital to know how much is too much, and how long is long enough to induce the nasty effects, giving rise to warn the community that herbal medications are not always safe, even if they are natural. Nevertheless, further observations and trials are needed to prove the herbal etiologies in humans.

CONCLUSION

Herbs have always been a constant source of medicines since the beginning of time as people used to medicate their ill. Locally, herbalism is rooted into the culture, and passed on through different generations. Hence, recognizing its toxic effects is of paramount significance as its therapeutic medicinal properties. *Ferula asafetida (Heltit)* is popular nation-wide, reports indicated its relation to Methemoglobinemia in infants.[10] However, we came to remark a new and genuine observation linking it to Aplastic Anaemia and toxic bone marrow suppression. We, hereby, urge physicians to be enlightened in regards to this relevance and help to educate their patients.

Ethical considerartions & irb approaval

A written consent was obtained and signed by the legal guardians of both children for full disclosure while maintaining strict confidentiality in respect to the patient medical information and images under the approval of King Fahad Medical City (KFMC) research centre

ethical committee. Under the umbrella of KFMC Institutional Review Board (IRB), this case was approved.

Data availability

The data that support the findings of the study are available from the corresponding author upon reasonable request.

CONFLICT OF INTEREST

All authors have no example conflicts of interest to disclose.

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Authors' contribution

FK; The primary author, attending physician and reviewing the whole manuscript.
AM Co-author, Co- Reviewing the whole manuscript.
AE and SJ; Co-authors, Planning the case report conception and design, reviewing relevant literature and the final writing.
MM; Co-author, Writing the case report scenario.
SR; Co-author, Obtaining the written and verbal consent.
TB and NT; Co-authors, Reviewing and writing the Labs.
AS; Co-author, Reviewing discussion.
MS; Co-author, Reviewing HMG course.
MG; Co-author, Reviewing conclusion, references and pictures.

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