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Pancytopenia in Epidemic Dropsy: A Case Report

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ABSTRACT:

Epidemic dropsy is caused by the consumption of mustard oil contaminated with argemone oil, characterized by pitting edema of the extremities, especially lower limbs; cutaneous erythema and local tenderness; Glaucoma and other visual field defects, leading to blindness; cardiac and respiratory problems leading to death are among the most severe manifestations. A family consuming self-cultivated contaminated mustard oil suffered from dyspnoea and pedal edema; 5 of them approached the tertiary center after the demise of two members, an elderly and a kid, at home. Out of those five, three were hospitalized in the medicine department, while 2 were admitted to the pediatric department. So here we report a case series of 3 patients, residents of Prayagraj Uttar Pradesh, India, who presented in March 2023 with all the classical features of epidemic dropsy (ED), all belonging to the same family admitted in the medicine department. They had variable presentations, but surprisingly, all of them had pancytopenia, all had AKI(acute kidney injury), all had a reticular hyperpigmented rash, all landed up in noncardiogenic edema but the one with underlying Perimembraneous VSD(ventricular septal defect) had increased severity, two had renal concretions, one had visual defect and the one using it topically too, had diffuse hyperpigmented skin and hair loss as well. The adulteration of oil with argemone was confirmed by nitric acid test and ferric chloride test. Patients felt improvement in conservative management. AKI improved in 45 days on average. This is the first case report having pancytopenia in all cases never found in any single family outbreak or multiple family outbreak of epidemic dropsy.

Keywords: *Epidemic Dropsy, Mustard oil, Argemone maxicana, AKI, Pancytopenia.*

1. Introduction

Epidemic dropsy is caused by the consumption of mustard oil contaminated with argemone oil. The seeds of the weed plant Argemone Mexicana mimic mustard seeds, and the season of blooming is the same. Besides, the flowers are the same color. Thus making the removal of weed cumbersome. Moreover, mustard oil is completely miscible with argemone oil.[1-4] Epidemic dropsy has been prevalent in the community for ages now. Evidence of this dates back to the Mughal armies being affected by several diseases, including dropsy. [5]. Traditionally, the use of this plant, *Argemone mexicana*, has been studied extensively. The seeds of this plant have been used as antidotes in snake poisoning. Other uses of the plant include dermatological use, cold sores, ophthalmic problems, controlling blood sugar levels, scorpion bites, and malaria fever. The use of this plant is not limited to its seeds, but literature shows data regarding several uses of the plant oil, leaves, and yellow juice.[6]

Epidemic dropsy is characterized by pitting edema of the extremities, especially of the lower limbs, cutaneous erythema, and local tenderness. Sanguinarine and dihydrosanguinarine are the toxins in Argemone (*katkar*) oil that are responsible for the pathogenesis causing enhanced permeability and leaking of proteinaceous plasma in interstitium and dilatation of capillaries resulting in anasarca, specifically oedematous feet. [7]

2. Case report

Out of a family of 7 members from Prayagraj, five presented to our hospital with bilateral pedal edema, hyperpigmented rash, and dyspnoea for two weeks; two of them were children. They

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all were receiving treatment from the local hospital for similar complaints, but two of the family members expired during the treatment before coming to our tertiary care center. Out of the surviving five, three were hospitalized in the medicine department, while two were admitted to the pediatric department. So here we report a case series of 3 patients belonging to the same family and residents of Prayagraj Uttar Pradesh, India, who presented in March 2023 with all the classical features of epidemic dropsy (ED). The family was primarily involved in agriculture and belonged to the lower middle class. The patient's age varied from 5 to 45 years. All the members of the family were consuming oil of mustard seeds cultivated in their own land for the first time in their life from last 1 month. The clinical details of all three cases are shown in Table 1.

Table 1: shows the clinical manifestations of all the patients

CASE	1	2	3
Age/Gender	35/male	30/female	25/male
Symptoms from the last 2 weeks	B/L lower limb swelling, chest pain &dyspnoea, diminution of Right eye vision	B/L lower limb swelling and dyspnoea on exertion	B/L lower limb swelling, dyspnoea on exertion
General examination	Pallor, B/L pitting pedal edema, and hyperpigmented rash over both legs, chest, and trunk were present.	Pallor, B/L pitting pedal edema, and hyperpigmented rash all over the body were present.	Pallor, B/L pitting pedal edema, hyperpigmented rash all over the body
Cardiac examination	pan systolic murmur present	WNL	WNL
Respiratory examination	Right sided pleural effusion	WNL	WNL
Refraction Right eye Left eye-	 6/24 6/9	 6/6 6/6	 6/6 6/6
Fundus examination Right Eye- Left Eye-	premacaluar hemorrhages with peripapillary superficial retinal hemorrhages superficial peripapillary hemorrhages with few para macular hemorrhages.	No Abnormality Detected in both the eyes	No Abnormality Detected in both the eyes

B/L bilateral

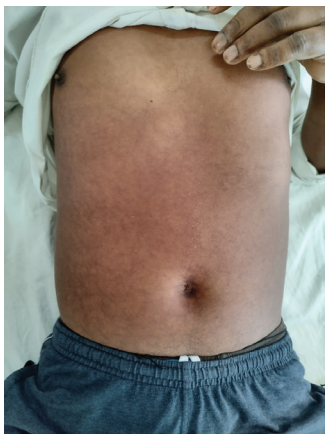

Fig 1a

Fig 1b

Fig 2

Fig1 & 2 show the skin manifestations of the cases.

Fig 1 (a) Case 1 hyperpigmented reticular Rash over chest and abdomen
Fig 1 (b) Case 1 showing B/L pedal edema with hyperpigmented reticular rash.
Fig 2 Case 3- showing hyperpigmented reticular rash over chest and abdomen and hyperpigmentation of hands and face due to topical application of contaminated mustard oil

Patients were thoroughly investigated, and reports are shown in Table 2.

Table 2: Showing Investigations of all the cases

Investigation (Reference range)	Case 1	Case 2	Case 3
Blood tests Hb(12-16 g/dl) TLC(4000-11000cells/mm³) Platelets(1.5-4.5lac cells /mm³) MCV(84-100fl) GBP Bone Marrow Aspiration Vitamin B12(normal Range= 189-889ng/dl/) Ferritin (30-333ng/ml) Folic acid(2.5-20ng/ml)	 6.1 3600 0.55 88.6fl Normocytic normochromic anemia Hypercellular 180 45 12	 5.2 2200 0.40 78.6fl Normocytic normochromic anemia Normocellular 320 289 23	 7.9 3200 0.80 72.6fl Normocytic normochromic anemia Normocellular 280 302 16
KFT Creatinine(<1mg/dl)	 2.35	 1.78	 1.92
Urine R/M 24 hour urinary protein	Proteinuria + 956mg in 24 hours	WNL 250mg in 24 hours	WNL 390 mg in 24 hours
USG Abdomen	WNL	WNL	WNL
2D ECHO	Global hypokinesis, Severe MR, TR with Perimemberaneous VSD Left to Right shunt	WNL	WNL
Xray chest PA view	Right sided pleural effusion	WNL	WNL
Nitric acid test Ferric chloride test	Mustard Oil from home tested positive for argemone oil contamination by Nitric acid test and ferric chloride test.		

B/L bilateral, WNL-with in the normal limit, Hb-hemoglobin, TLC-total leucocyte count, MCV-mean corpuscular volume, GBP-general blood picture, Urine R/M- routine and microscopic, KFT-kidney function test, USG-ultrasonography, 2D ECHO-2-dimensional echocardiography, MR-mitral regurgitation, TR-tricuspid regurgitation, VSD-ventricular septal defect, +present, PA-posterior-anterior view.

3. Differential Diagnosis:

Food poisoning was the foremost differential, as all the members of a single family were involved. Water contamination was ruled out as other families residing around were using water from the same water supply, and none suffered. Hypoalbuminemia, congestive heart failure, wet beriberi, and nephrotic syndrome have similar clinical presentations as dyspnoea and pedal edema, but none of the above investigating reports favored. Diagnosis of noncardiogenic edema, pancytopenia, and AKI(acute kidney injury) was made in all three cases, besides a component of CHF(congestive heart failure) was seen too and more evident in case 1 as case 1 had Ventricular Septal Defect and retinal hemorrhage too was seen in Case 1.

Nitric acid test was done in our own biochemistry lab by us in which 5ml of adulterated oil was mixed with equal amount of nitric acid and was shaken. On standing acid layer turned orange. (As shown in Figure 3).

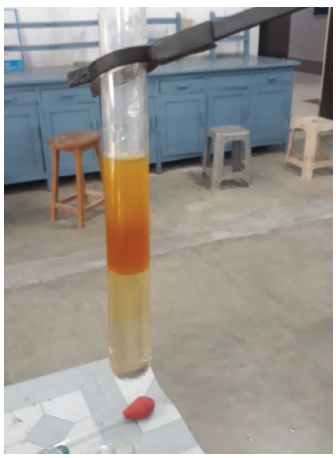

Figure 3: showing Nitric Acid test positive –orange, suggesting the presence of argemone oil

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Ferric chloride test-2ml oil and 2ml of concenterated HCL(hydrochloric acid) and heated in water bath at 33.5-35C for 2minutes, then 8 ml of ethyl alcohol added and ferric chloride was added and again heated for 10 minutes. Orange red precipitate was formed.

Thus, both tests suggested adulteration of the mustard oil with argemone Mexicana.

Levels of toxins in blood could not be tested due to nonavailability of tests.

4. Treatment

Cases were notified to the District Chief Medical Officer(CMO), and they visited the patients to interview, and surveillance was done at the hospital bedside beside their village residence area.

Case 1: was managed on IV antibiotics and Inj furosemide 40mg IV 8hrly, Tab Metoprolol 25 BD. The patient also required moist O2 inhalation at 2l through a Flexi mask for the first 3 days; then, he was off oxygen. A total of four units of PRBC were transfused. Injection of Vitamin B12 was also given. The hospital stay was for 40 days, and he was discharged on Tab Metoprolol 25 BD, Tab (Torsemide+spironolactone) 10/50 OD.

Case 2: A total of 2 units of PRBC were transfused and were managed on IV antibiotics and Inj Furosemide for 7 days only. The patient got symptomatically better after a blood transfusion. The hospital stay was 15 days. The case was discharged on Hematinics.

Case 3: No PRBC transfusion was required in case 3, and it was managed with diuretics for 7 days only. The hospital stay was 10 days.

All the three patients were given Tab Vitamin C 500 BD, Tab Zinc 50 OD, Tab B Complex BD and Tab calcium 500 BD.

5. Discussion

Dropsy is a disease that usually occurs in epidemics; isolated cases are seldom seen and reported [8]. Cases of epidemic drops are seen in northern regions of India, such as Uttar Pradesh, as in southern regions, coconut oil is consumed [9,10].

Epidemic Dropsy is seen in poor socioeconomic people as they cannot afford high-quality edible oils that are commercially tested prior with AGMARK(Agriculture Mark- Agriculture and Marketing Advisory To the Government of India, is a third-party guarantee for agricultural product) mark approving to be accordance to Indian standards. Confirmation of the adulterated oil is cumbersome, and detection of edible mustard oil being consumed necessitates laboratory investigation. Adulteration with even 1% of Argemone oil can produce manifestation. [11]

The reasons for this outbreak being restricted to a particular family can be explained as the contamination of mustard seeds with argemone seeds that occurred at the household level, where the mustard oil was extracted from the seeds of the plants cultivated on their own land. The family's low socioeconomic status and lack of knowledge prevented them from availing good quality edibles, and poor literacy was responsible for their ignorance regarding adulteration in mustard seeds being contaminated with argemone seeds, which was the source of the current outbreak. Target organs for Argemone oil poisoning include the gastrointestinal tract, heart, liver, lungs, kidney, and serum, as sanguinarine can stay in these sites for longer than 4days.[7]Dropsy patients have low levels of antioxidants, especially vitamins E and A.[12]

Sanguinarine causes inactivity of cytochrome P-450, and accumulation of sanguinarine further leads to its cumulative toxicity.[13,14] Additionally, sanguinarine acts on the Na+-K+-ATPase pump in intestinal cells, resulting in glycogenolysis and causing an accumulation of pyruvate in the blood. A similar effect is seen in the heart, which may provoke cardiac failure.[15] The commonest presentation of Argemone oil poisoning is an acute, bilateral lower limb swelling, which was found in all of our cases. Nausea, vomiting, diarrhea, mild liver dysfunction, and hepatomegaly are a frequent feature found in almost all patients, but none was seen in any of the members of this family in our case study. In extreme cases, glaucoma and even death due to cardiac arrest have been encountered.

The majority of cases reported are from groups of families, and outbreaks in single families are less in the medical literature.

Most of the cases reported had diarrhea at the onset. Surprisingly, none of our patients had diarrhea all through the course. Sunil Kumar Rao et al. in 2019[16] also reported epidemic

dropsy in a single joint family with none of the patients having diarrhea. All the patients presented with dyspnoea at the onset of pedal edema and the probable mechanism was increased permeability in capillaries due to sanguinarine. Pleural effusion was seen in case 1, who had additional congenital heart disease, i.e. Perimemberaneous VSD, and was diagnosed incidentally on Echo being indicated because of an alarming murmur he had on clinical physical examination and as a workup for dyspnoea and pedal edema even though the probable mechanism is noncardiogenic edema [17].

There is single case report in Epidemic dropsy having manifestation of AKI at the onset[18] and that too without any prior dehydrating illness like diarrhoea and vomiting in medical literature similar to that which is seen in our study and our all patient suffered from it which was reversible and improved on an average of 45-60 days and none had any dehydrating manifestation like vomiting or diarrhoea prior to it.

Regarding vision diminution, case 1 had macular hemorrhages with peripapillary superficial retinal hemorrhages in the right eye on fundoscopy with 6/24 refractive error and superficial peripapillary hemorrhages with few para macular hemorrhages in the left eye on fundoscopy with 6/9 refractive error. Kamal Singh et al. reported retinal abnormality in their case study as superficial retinal hemorrhages were present in both eyes in a boy of 12 yr and soft exudates in the left eye in a 55 yr old male in an outbreak in a single family[17]. Sunil Rao reported subconjunctival hemorrhage in one of the members of his case report.[16] Raised intraocular pressure is noticed in 0–12% of cases, and retinal hemorrhage, if present, requires urgent surgical intervention to prevent blindness [19, 20]

Our all the members of the family had pancytopenia which has never been seen in any case reports. Other etiologies of pancytopenia, was searched. Our cases didn't have hepatosplenomegaly; nutritional cause was ruled out as just only one case had borderline low Vitamin B12, rest all folate and ferritin were normal. MCV was normal in all the patients .Bone marrow disclosed no clue in any.

In our case, case 3 also had hyperpigmentation of the skin and increased hair loss as he was applying the oil to his face and hair. This darkening might be attributed to the topical application of oil to the face, leading to transcutaneous absorption of argemone oil and sanguinarine toxicity. In some of the case reports, red macules and telangiectasia have been documented, but patchy reticular hyperpigmentation in all the members of the family and diffuse hyperpigmentation because of the effect of topical application is the first time seen and reported here only.

Organs of predilection for Argemone oil include the gut, cardiac, hepatic, pulmonary, kidneys, and serum because sanguinarin persists in these sites for longer than 4days.[7].Dropsy patients have low antioxidants, especially vitamins E and A.[12].

Recovery time is about 3 months.[17]. Our patients had a history prior to admission of 15 days and remained hospitalized for one and a half months till they became symptomatically relieved, so the total duration of hospitalization and significant improvement was 2 months. The patients came in for follow-up, and total improvement took nearly 3 months.

The differential diagnosis to be considered includes nephrotic syndrome, congestive cardiac failure, myxoedema, and anemia, and all of these are usually not seen in all the family members simultaneously, except one more differential beriberi, which was ruled out as no alteration in the usual routine diet was seen. The only change in lifestyle was a change in oil consumption, and the symptoms appeared after around 15 days of consumption. In a similar case report, symptoms started after 15 days of consumption.[17]Toxins in water were not considered to be attributable as they were not seen in members of the localities who all consumed water from the same water supply. A correct diagnosis requires a high index of suspicion, as the disease is rarely seen in regular clinical practice.

As anemia was normocytic normochromic and was found in all the cases, the probable cause might be bleeding in

the gut, inactive bone marrow, and decreased red blood cell survival.[21]

Nitric acid testing and ferric chloride are the two easily done lab tests[22]

Nitric acid Tests can detect even if the concentration of argemone is as low as 0.25%. Nitric acid and Ferric Chloride Tests were done in the oil brought from their home. If argemone oil

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is present, an orange-red precipitate is formed, as in our study.

Paper Chromatographic Method – This is supersensitive, detecting as low as 0.0001% Argemone oil contamination.

The foremost need is to withdraw the culprit oil. Avoidance of exertion and leg dangling must be advised. Judicious and cautious use of diuretics with vigilance of hypovolemia and electrolyte imbalance is needed. The pleural effusion of case 1 improved with diuretics. Replenishment of antioxidants (vitamins A, C, E), Vitamin B1, Protein, and calcium must be done. AKI(acute kidney injury), in our cases, didn't need dialysis. Patients were discharged on significant improvement, and case 1 was referred to an eye surgeon for his retinal hemorrhage. Poor prognostic factors like ARDS (adult respiratory distress syndrome), heart failure, and AKI were which were seen in our cases, and besides pneumonia, can be complicated with medical literature showing a 5% mortality rate.

Suspiciousness and vigilance in the right direction is must for detection of argemone oil in mustard oil and ruling out differentials is must to reach the final diagnosis of epidemic dropsy.Timely Blood transfusions in our cases of pancytopenia was very much warranted.

Our patients were having a multitude of life-threatening manifestations such as ARDS, CHF, AKI, and debilitating vision diminution to the extent of blindness and pancytopenia.

6. Conclusion

Strong suspicion and sharp vigilance in a group of people belonging to a single family presenting with dyspnea and pedal edema unmasked the diagnosis of Epidemic dropsy with grave complications of ARDS, AKI, CHF, pancytopenia and retinal hemorrhages, and this life-threatening situation could be salvaged. This case report further highlights the need to educate farmers regarding food adulteration.

Public and Patient Involvement

The diagnosis of epidemic dropsy should be strongly suspected if there is a simultaneous complaint of dyspnea and bilateral pedal edema within the group of people sharing the same kitchen in a single family, especially where the preferred edible oil is mustard oil. Patients and the Public, especially farmers, must be educated about the Food Adulteration Act, argemone weed growing rampantly in the same season amongst mustard plants and mimicking in all aspects in appearance and smell, and the need to prevent dropsy.

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