

Changing Pattern of Epidemic Dropsy in North India

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Abstract

Background: Epidemic dropsy occurs due to ingestion of mustard oil contaminated with oil from *Argemone mexicana*, leading to edema and tenderness of the abdomen, upper and lower limbs. In this study, clinical profiles of patients presented with epidemic dropsy in north India are described.

Methods: This was a prospective study of patients presented with epidemic dropsy to the emergency department of Nehru Hospital, during the period from March 2004 to December 2011. Inclusion criteria were patients presenting with tender bilateral pitting leg edema and dermal telangiectasia. Clinical and laboratory data of patients were entered into case record forms at the time of presentation until discharge from the hospital.

Results: Leg edema was the principal symptom in our series, and was in concurrence with current literature. Erythema has only been reported in 35-82% of published series, though it was present in all of our patients. Similarly, features such as diarrhea, hepatomegaly and anemia were more frequent in our cases compared to the literature. Furthermore, pancytopenia which was documented on peripheral blood counts in 54% of our cases has never been reported before.

Conclusion: Epidemic dropsy should be considered in patients presenting with progressive erythema, edema, and tenderness of the limbs who had a history of consumption of mustard oil and confirmation of *Argemone* oil contamination according to laboratory tests.

Keywords: *Argemone mexicana*; Dihydrosanguinarine; Dropsy; Poisoning; Sanguinarine

INTRODUCTION

Mustard oil (*Brassica nigra*) which is derived from mustard seeds is commonly used as a cooking medium in many parts of India. While harvesting, the mustard seeds become contaminated with the wild seeds of *Argemone mexicana* (Mexican prickly poppy) that commonly grows alongside mustard plantations (1,2). The main alkaloid of *Argemone* oil is toxic, and belongs to the class of benzophenanthridine group, namely sanguinarine and dihydro-sanguinarine (1-6). Its ingestion causes a progressive leg edema, also known as epidemic dropsy (1).

The first record of epidemic dropsy was in Calcutta in 1877 (3). Since then, numerous outbreaks have been recognized and reported all over India (1). The most recent was the New Delhi epidemic in 1999, where 3000 people had to be hospitalized for treatment and eventually caused 60 fatalities (2,5). Epidemiological investigations revealed that all affected individuals belonged to the lower socioeconomic strata of society and were using mustard oil for cooking that was purchased from local vendors. Epidemic dropsy has also been reported from Fiji Islands, Madagascar, Mauritius and Cape Districts of South Africa, where wheat flour was contaminated with *Argemone* oil (5).

In this study, clinical profiles of a series of patients presented with epidemic dropsy in north India are described.

METHODS

This was a prospective study of patients presented with epidemic dropsy to the emergency department of Nehru Hospital, postgraduate Institute of Medical Education and Research, Chandigarh, India during March 2004 till December 2011. Inclusion criteria were cases with bilateral tender pitting leg edema cases along with multiple cutaneous telangiectasia. All admitted cases underwent a detailed history taking, general physical examination and laboratory investigations such as complete hemogram, serum biochemistry, renal and liver function tests, chest X-ray, electrocardiogram, echocardiogram and urine analysis. Collected data were analyzed using Microsoft Excel spreadsheet (Microsoft Corp., Redmond, WA, USA). Using the nitric acid test, the contamination of m(used in cooking) with *Argemone* oil was assessed for all admitted cases.

RESULTS

Index case: A 47-year old man presented to the emergency services with a month history of a burning sensation, swelling and redness over the feet. He also had a 20-day history of dyspnea and denied the presence of any chest pain, productive cough, orthopnea, or paroxysmal nocturnal dyspnea. He also complained of a recent-onset diarrhea with small volume and semi-formed stools. There

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was no fever, tenesmus, abdominal pain, distension or vomiting. He reported that his wife and daughter had a similar erythema and edema of the lower limbs, and his wife had subsequently died following a lower gastrointestinal bleeding. His daughter was also reported to the emergency services with similar painful leg edema but without any respiratory symptoms. She underwent detailed investigations on outpatient basis, recovered without any particular complication and was followed-up till her father's discharge from the hospital. On further medical history, the patient admitted that his family had been harvesting mustard seeds on his farm, and had used the oil extracted from the seeds as a cooking medium.

The patient was cooperative, sitting in a bed, and breathing in supplementary oxygen. Vital signs were abnormal, with the pulse rate at 110 beats per minute, a raised jugular venous pressure (10 cm above the sternal angle), respiratory rate at 28 breaths per minute, and a blood pressure of 110/50 mmHg. The patient was pale, but no jaundice, cyanosis, clubbing or lymphadenopathy was detected. Examination of the lower limbs revealed pitting edema up to the lower abdominal wall, and tenderness in the same distribution. The skin on his forearms, legs, lower abdomen and back had a lacy dermal venous prominence, with numerous telangiectasia and erythematous macules (Figure 1). Abdominal and neurological examinations were normal, whereas the auscultation of his chest revealed an S₃ gallop rhythm and rales of bilateral base of lungs. The results of his laboratory and radiographic investigations are summarized in table 1.

The presence of *Argemone* oil contamination was confirmed using the qualitative nitric acid test (3). This test includes addition of 5 ml mustard oil to an equal volume of nitric acid and letting the mixture remain. Subsequently, the acid layer turns yellow, orange-yellow, or crimson, depending upon the amount of *Argemone* oil which is

present in the sample. The test is sensitive to a concentration of >0.25% *Argemone* oil. A positive nitric acid test in this case allowed us to make the diagnosis of epidemic dropsy.



Figure 1. Cutaneous telangiectasia with red erythematous macules

Table 1. Results of laboratory and radiographic investigations of the index case

Investigations (Normal Values)	Results
Hemoglobin (15-17 g/dL)	7.3 g/dL
White blood cell count ($4-11 \times 10^3/\mu\text{L}$)	$2.2 \times 10^3/\mu\text{L}$
Platelet count ($150-450 \times 10^3/\mu\text{L}$)	$31 \times 10^3/\mu\text{L}$
Reticulocytes (< 2%)	2%
Sodium (135-145 mEq/L)	144 mEq/L
Urea (20-40 mg/dL)	40 mg/dL
Creatinine (0.6-1.1 mg/dL)	1 mg/dL
Aspartate aminotransaminase (20-40 IU/L)	28 IU/L
Alanine aminotransaminase (<40 IU/L)	25 IU/L
Albumin (3.5-4.5 g/dL)	3.6 g/dL
Peripheral blood film analysis	Mild red blood cells anisocytosis and microcytosis
Chest X-ray	Prominent upper lobe pulmonary veins, normal heart size
Electrocardiography	Sinus tachycardia (110 beat per minute), Normal axis, PR interval (0.10 milliseconds), corrected QT (0.42 milliseconds), normal QRS complex and T waves
Abdominal sonography	Hepatomegaly (16 cm), no alterations in liver echotexture, no free fluid

Table 2. Clinical features of major series of patients presented with epidemic dropsy*

	Study				
	Tandon et al.; 1975 (Delhi and Uttar Pradesh, n=45)	Gomber et al.; 1992 (Delhi, n= 30)	Singh NP et al.; 1998 (Delhi, n=212)	Singh R et al.; 1999 (Nepal, n=26)	Current study; 2004-2011 (Punjab and Haryana, n=11)
Edema (%)					
Leg	100	100	100	100	100
General	20	26	-	-	27
Erythema (%)	35	80	75	82	100
Tenderness (%)	22	70	63	88	100
CHF (%)	2	6	14	29	27
Diarrhea (%)	73	36	51	82	54
Hepatomegaly (%)	24	10	34	41	54
Anemia (%)	100	46	-	88	46
Pancytopenia (%)	-	-	-	-	46

*Data were extracted from references 14 to 17.

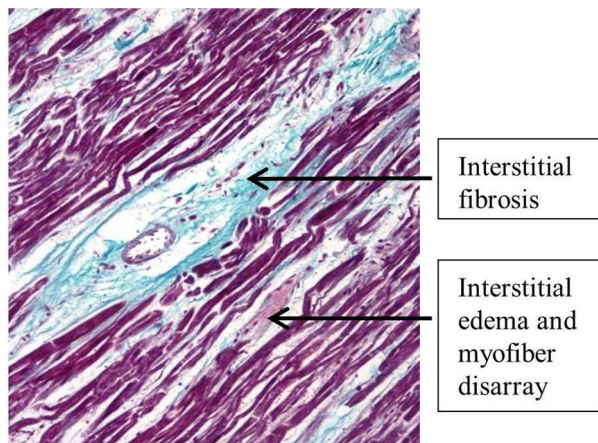


Figure 2. Microscopic view of the heart which shows myocardial fibers disarray, interstitial edema and fibrosis (greenish-blue on Masson’s trichrome stain; magnification×100)

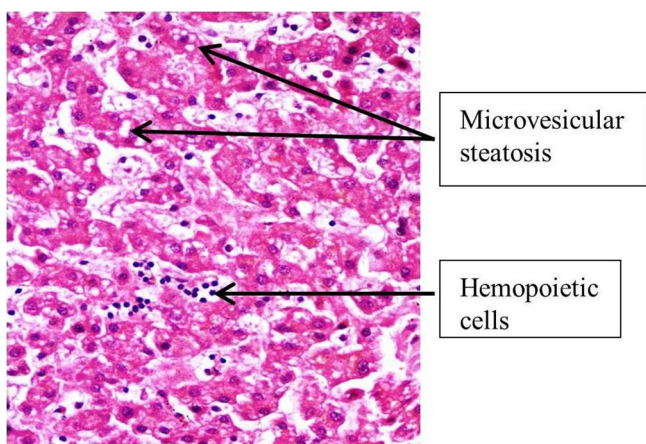


Figure 3. Microscopic view of liver which shows microvesicular steatosis and extramedullary hematopoiesis (magnification × 100)

The high output congestive cardiac failure was treated with salt and fluid restriction, bed rest, oxygen supplementation, and 40 mg/day of furosemide. Over the next 5 days, he sustained a rapid drop of his hemoglobin levels to 5 g/dL, and received a transfusion of 4 units of packed red cells. Consequently, his clinical condition improved gradually and he was discharged on the 11th day post-admission. At discharge, the erythema and edema of the lower limbs was still evident, while the edema of the upper limbs had completely resolved.

Other Cases: We prospectively studied 10 other cases (6 women and 4 men, from 4 different families) presented with epidemic dropsy to the Nehru Hospital, Chandigarh. Main clinical features at the presentation are summarized in table 2 and compared with similar outbreaks of epidemic dropsy. All patients were presented during the period of June to August. The mean (SD) age of all cases was 29 (9) years (range = 19-49). Echocardiography was carried out in all cases which showed changes consistent with dilated cardiomyopathy in only one patient. Six patients had anemia (hemoglobin range = 4.7-7.7 g/dL), leukopenia (range = 2.2-3.9×10³/μL) and thrombocytopenia (range = 30-56×10³/μL), and all of them received packed red cell transfusions.

Five patients were treated with folic acid, vitamin B and E supplementations, and a protein rich diet. The remaining six were treated with a high protein diet and folic acid only. Patients who presented with congestive cardiac failure (n=3) were treated with fluid restriction, salt restriction, and furosemide. The mean (SD) hospital stay of the six admitted cases was 8 (5) days (range = 3-15 days), and the remaining five cases were followed up as outpatients. Three cases died, two of them due to congestive cardiac failure and the other one due to lower gastrointestinal bleeding, which gave our patients with epidemic dropsy a mortality rate of 27%.

Autopsy and microscopic examination of one patient revealed that all the cardiac chambers were dilated without any mural thrombi and the myocardial fibrils were in disarray with interstitial edema (Figure 2). Cardiac myocytes

displayed anisonucleosis, and there was patchy perivascular and interstitial fibrosis. Gross examination of the liver, lungs and spleen showed congestion. On microscopic evaluation, alveolar edema was observed in the lungs, in addition to a focal steatosis and extramedullary hemopoiesis in the liver (Figure 3), and features of acute tubular necrosis in the kidneys.

DISCUSSION

Argemone mexicana (family: *Papaveraceae*), also known as Mexican Prickly Poppy, a plant widely present in Mexico and North America and has been naturalized to India from the West Indies following trade practices (1,2,5,6). The seeds of this plant are dark brown in color and can reliably be distinguished from the seeds of brown mustard (*Brassica campestris*), though closely resemble the seeds of dark mustard (*Brassica nigra*). As mustard plantations are often situated close to areas where *Argemone mexicana* grow, the seeds of *Argemone mexicana* are inadvertently harvested along with the mustard seeds, thus contaminating the extracted mustard oil (5).

The mechanism of cellular damage caused by *Argemone* oil in patients with epidemic dropsy is shown to be through the increased generation of free radicals, coupled with a malfunctioning antioxidant system (5-9). Normal human cellular metabolic processes generate free radicals as by-products of biochemical redox reactions, and the active antioxidant systems help to scavenge these free radicals. Upon a compromise of the antioxidant system, accumulation of excess free radicals leads to extensive damage to various macromolecules such as proteins, lipids and nucleic acids. In epidemic dropsy, the main causative agents for this damage are the toxic alkaloids, known as Sanguinarine and Dihydrosanguinarine which can be found in *Argemone* oil. Moreover, these alkaloids have a direct toxic effect on cells. Possible mechanisms are inhibition of Na-K ATPase activity, reduction of ATP production due to reduced glycogen levels, raised Interleukins 1 and 6, elevated TNF- α level, and an increased production of reactive oxygen and nitrogen species which lead to DNA damage and apoptosis (1,5-9). All these mechanisms cause endothelial damage, increased capillary permeability, leakage of protein rich fluid into the interstitial spaces, and vascular damage (8-10).

A study of 21 patients with epidemic dropsy demonstrated a compromised antioxidant status leading to an accumulation of free radicals and increased lipid peroxidation (8). This reaction resulted in an enhanced osmotic fragility of erythrocytes and hemolysis. Other examples of *Argemone* oil-induced cellular damage includes protein modification by incorporation of Carbonyl residues, and a depletion of glutathione (6,7). This could be the explanation for blood pancytopenia seen in our case series.

Although, Sarkar et al. in 1948, conclusively established the link between the alkaloid Dihydrosanguinarine found in *Argemone* oil and epidemic dropsy (11), yet, this knowledge has not led to an eradication of the disease (5,6,12). Fortunately, in India, epidemic dropsy has not been detected in epidemic proportions in the last decade due to an increase in legislation and awareness. The 'Food Safety and

Standards of India' (FSSI) have laid down norms for marketing and sale of refined edible vegetable oils in India. According to FSSI, mustard oil for sale must be free of *Argemone* oil (13) and selling mustard oil contaminated with *Argemone* oil is liable to be punished by law. These legislative measures have resulted in a change in the epidemiology of the disease. Epidemic dropsy now affects families involved in cultivating, harvesting, and consuming mustard oil that possibly get contaminated with *Argemone* oil during the harvesting of mustard. As the harvesting season for mustard is usually from February to March, the disease is mostly observed between the months of March and July (1,6,14). This trend was evident in our study, with all of the cases presenting during the summer months.

Review of literature suggests that pitting edema is the main clinical feature in patients with epidemic dropsy, and this finding was corroborated by the results of our study. Other cutaneous findings such as erythema and skin tenderness are the features which were variably reported in previous studies (35-82% and 22-88%, respectively) (14-17), however, these two dermatological manifestations were present in all of our cases (Table 2). Other skin changes such as widespread telangiectasis, erythrocyanosis, mottling and blanching were seen in three of our cases. The histopathological basis of these dermatological signs is an edema of the dermis and the deposition of an acellular hyaline material in the wall of the blood vessels within the dermis, along with the presence of vascular thrombi (18). In all of our observed cases, the dermal manifestations persisted until discharge. Previous studies on epidemic dropsy suggest that these dermatological changes, particularly the erythema and edema, continue to persist for a period of 3-6 months (14-17).

In our series, cardiac failure was found in 27% of patients which is comparable to the reported figures in the literature of 2-29% (14-17). Cardiac failure is frequently exacerbated by concomitant anemia. Autopsy studies of patients with epidemic dropsy who died from congestive cardiac failure demonstrated a ventricular wall thinning and separation of the cardiac muscle fibers by dilated blood vessels (4). The results from the autopsy performed on one patient in our study revealed similar findings to those reported by Verma et al (19). Amongst clinical manifestations, diarrhea was found in 54% of our cases and was reported in 36-82% of previous studies (14-17). This complication is due to the extravasation of protein rich fluid from the toxin-induced vascular damage to the intestinal lamina propria (14-17). Hepatomegaly was recorded in 10-41% of earlier cases that was also present in 54% of our patients. Although it has been thought that hepatomegaly in patients with epidemic dropsy is a complication of congestive cardiac failure, yet, only 36% of our patients with hepatomegaly had evidences of cardiac failure (Table 2). In our study, pancytopenia was seen in six cases. Anemia is a common feature of epidemic dropsy (14,15,17); however, pancytopenia has never been reported so far.

Withdrawal of the offending agent - the contaminated mustard oil - is the cornerstone of management, being vital to limit the progression of symptoms. A direct correlation

between the amount of *Argemone* oil consumed and the severity of symptoms may account for the varying severity of disease within members of the same family in our study. Symptomatic treatment was provided for all cases in this study. All 3 patients with congestive cardiac failure were treated with bed rest, oxygen supplementation, diuretics and fluid restriction. In addition, oral folic acid supplements were prescribed for patients with hemolytic anemia. A review of the literature based on animal experiments in rats has elaborated upon the use of a high protein diet and vitamin supplementation to replenish the depleted antioxidant levels, which are mainly riboflavin, tocopherol and retinol (1,2,5,6,11). We followed the aforementioned recommendations for the first five patients who admitted to our hospital; however, due to a lack of observed benefit, we abandoned such treatment plan for the remaining six. In the absence of definite randomized control trials, such recommendations remain speculative.

LIMITATIONS

In this study, the concentration of Sanguinarine and Dihydroanguinarine in blood, urine and the contaminated mustard oil was not evaluated.

CONCLUSION

Although epidemic dropsy still exists in India, its mode of presentation has changed from an epidemic to a sporadic pattern. This poisoning should be suspected in patients presenting with edema, erythema, tenderness of the limbs, and a collection of these symptoms within farmer families. Epidemic dropsy can be confirmed by a laboratory exam of contamination of mustard oil with *Argemone* oil (nitric acid test). Effective strategies to eradicate this poisoning involve public education, mandatory quality inspections, and detection of possible contaminations.

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