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Aplastic Anemia in Western India: An Etiologic Enigma

Nutan Joshi[1], Namita Padwal[1], Milind Patil[2], Niteen D Karnik[1] and Louis Aledort[3]*

[1]*Department of Medicine, Lokmanya Tilak Municipal Medical College and LTM General Hospital, India*

[2]*Department of Pathology, Lokmanya Tilak Municipal Medical College and LTM General Hospital, India*

[3]*Department of Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, USA*

Abstract

Aplastic anemia is a serious hematological disorder, three times more common in Asia than West. At LTM General Hospital, Mumbai (Western India), we saw three cases in young females within a week. We are presenting these cases to highlight the clustering of a relatively uncommon condition in young females where etiology is an enigma. Treatment such as Anti-Thymocyte Globulin (ATG) is not always available despite its very good success rate, especially in young patients. These three patients couldn't receive Anti Thymocyte Globulins (ATG) because of financial issues. Apart from being a pan Indian issue, aplastic anemia, with its etiological uncertainties and morbidity poses challenges in management worldwide. It is important that the scientific community addresses to the possibility of a common unidentified etiology, so that it may be treated and possibly prevented.

Introduction

Aplastic anemia, a rare disorder in most of the world, is more prevalent in Asia [1-3]. Rarely is it due to congenital disorders like Fanconi's anemia or Shwachman-Diamond Syndrome. Genetic predisposition has only been reported in Korean population [2]. Though many etiologic factors are postulated, it is difficult to identify the etiology in a given patient [2-4]. The age wise distribution is biphasic with peaks between the ages of 15 to 25 years and after age 60 years [4]. In one week, in our hospital, we encountered, three young women who presented with pancytopenia and were diagnosed as aplastic anemia. ATG is now approved as treatment of choice for aplastic anemia in the absence of feasibility of an allogenic Bone Marrow Transplant (BMT). The 6 month response rate of first course of ATG is around 70% [5]. These three cases are symbolic of dearth of information on etiology of aplastic anemia and socioeconomic hurdles for optimal therapeutic interventions.

Materials and Methods

All the investigations in these three patients were done at LTM General Hospital, Sion, Mumbai, India.

Case Series

Case 1

A 13 years old female, school student, from tribal area of Maharashtra, belonging to lowest socioeconomic strata came to Medical OPD with complaints of easy fatigability for last one and half years. There was no history of jaundice, loss of weight or appetite. She had history of fever one and half years back, when she was given herbal medicines from a local doctor after whom she recovered 6 weeks later, patient began to require monthly blood transfusions; the frequency doubled in past two months. There was no family history of similar illness.

On examination, her pulse was 96 beats per minute; she was normotensive and had severe pallor. There was no hepatosplenomegaly. Her investigation profile is outlined in Table 1.

BM trephine shows markedly reduced cellularity with replacement of trabecular spaces by mature adipose tissue. Interstitium shows infiltration by sparse amount of lymphocytes and occasional plasma cells. There is trilineage suppression of erythroid, myeloid and megakaryocyte series features suggestive of aplastic anemia (Figure1).

She was put on T. Cyclosporine 100 mg and Danazol 100 mg, both twice daily. She also received 3 Packed Red Cell (PRC) transfusions during this admission. Relatives insisted on discharge so she was discharged with CBC Count of: Hb 6 gm %, TLC 3000/µl and platelets of 24000/µl with instructions to follow up.

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Correspondence:
Nutan Joshi, Department of Medicine, Lokmanya Tilak Municipal Medical College and LTM General Hospital, Mumbai, 400022, India,
E-mail: nutanjoshi27@gmail.com

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Table 1: Investigation Profile.

	CASE 1	CASE 2	CASE 3
Hb (gm%)/RBC Count (millions per micro liter)	3/1.8	5.7/1.86	1.6/0.47
Reticulocyte Count (%)	0.2	0.11	2.3
MCV (FL)/MCH (pg)/MCHC (g/dL)	82/30/34	87.6/30.5/34.8	95.5/33.5/33.1
Total Leucocyte Count (per microliter)	900	1400	2900
Neutrophils/Lymphocytes/Monocytes/ Eosinophils in %	60/35/4/1	5/88/6/1	40/51/9/0
Platelet Count (per microliter)	20000	4000	1000
Peripheral smear	Normocytic normochromic	Normocytic few macrocytes, Normochromic	Normocytic, normochromic
ESR mm/hour	106	66	55
Sr Iron/TIBC (both in mcg/dL)	98/248	94/288	102/233
T. Bilirubin (Direct bilirubin) (mg/dL)/ ALT/ AST (IU/L)	0.6 (0.2)/26/32	0.6 (0.3)/22/24	0.8 (0.2)/34/29
BUN/Creatinine (mg/dL)	12/0.7	14/0.9	14/0.8
HIV/HBsAg/HCV	All three non reactive	All three non reactive	All three non reactive
ANA	Negative	Negative	Negative
PNH profile	Could not be done due to financial constraints	Negative	Negative
Sr. Vitamin B12 levels (pg/ml) N: 187-883	Not done	>2000	>2000

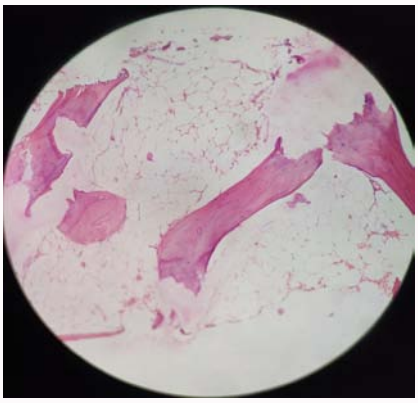

Figure 1: Bone marrow biopsy of patient 1.

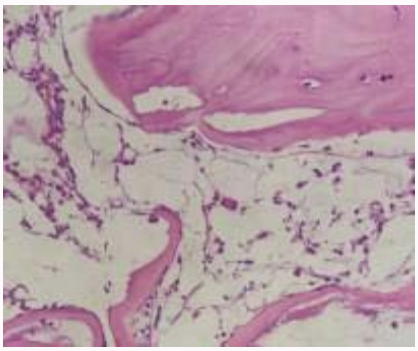

Figure 2: Bone marrow biopsy of patient 2.

Case 2

A 19 year old lady, resident of Mumbai, came with complaints of, intermittent fever and fatigue since 6 weeks, multiple petechiae and black colored stools since 10 days. She denied any breathlessness, chest pain or pedal oedema. There was no history of intake of any proprietary medicines. There was no past or family history of similar illness. Her physical examination was noteworthy for tachycardia, pallor and petechiae over extremities. Her investigations are outlined in Table 1. Serology was negative for dengue, malaria, leptospirosis and typhoid.

BM aspirate and biopsy revealed hypo cellular marrow without any dysplasia and features were consistent with aplastic anemia; however few hematopoietic foci were preserved (Figure 2).

Patient was transfused PRCs and platelets multiple times. Her husband was explained about the treatment options of ATG or BMT. Her family was arranging for the finances; financial constraints delayed initiation of ATG treatment. She was started on T. Cyclosporine and T. Danazol in standard doses. Meanwhile patient missed her menses and was found to be 5 weeks pregnant. She had spontaneous abortion in 6th week of her pregnancy. Her counts continued to decrease. Her CBC trend was as follows (Hb gm %/WBC per µl/Platelet per µl) → 5.2/1200/5000 (day 12), 6.1/1100/7000 (day 20), 6.3/600/4000 (day 30). She received broad spectrum antibiotics, antifungals, inj Granulocyte Colony Stimulating Factor. She continued to deteriorate and died due to febrile neutropenia, sepsis and pancreatitis in MICU on day 37 of admission. The post mortem revealed multiple thin walled abscesses in lungs and spleen with evidence of acute pancreatitis.

Case 3

A 25 years old housewife came with complaints of weakness, menorrhagia and occasional oral bleeding since last 4 months. She had an episode of acute febrile illness 4 months back, diagnosed as dengue by a local doctor. She gave history of receiving 2 Random Donor Platelets (RDP) and 2 PRCs in last 4 months. She didn't give history of joint pain, rash, alopecia or jaundice. Her previous delivery 2 years back was uneventful. On examination, pulse 100/min, BP 104/78 mmHg. Systemic examination was normal. Her further investigations profile is shown in Table 1. Her dengue IgG was positive. Ultrasound of abdomen was normal. BM Aspiration and Biopsy showed features consistent with aplastic anemia and there was no evidence of hemophagocytosis on bone marrow. Patient was given options of BMT and ATG. She was started on Tab Cyclosporine and Danazol in standard doses. Patient needed frequent blood and platelet transfusions. She was discharged after 3 months of indoor stay with the following CBC, Hb 7 gm %, TLC 2200/µl and platelets

10000/µl. Finances for ATG are in process.

Discussion

These three cases, by no means unique, are prototypic of what we see in India and Pan - Asia, where aplastic anemia is rarely due to a known predisposing etiological factor. In our three cases, one had history of prior ingestion of herbal medicine. Herbal medicines may contain certain toxins, like phenylbutazone, which may cause bone marrow failure [6]. Our second case had unplanned pregnancy and developed fatal sepsis following spontaneous abortion. Our third case had history of dengue prior to aplastic anemia. Dengue fever is rare cause of aplastic anemia [7]. Dengue can also induce Hemophagocytic Lympho Histiocytosis (HLH); however this was excluded on bone marrow biopsy.

The literature is replete with cases [1-3]. However the basic science literature has not yet yielded either etiologic factors or factors that could prevent the transition of normal bone marrow to an aplastic one. In addition, the financial infrastructure of India today, despite its commitment to healthcare, doesn't support extraordinarily successful therapeutic intervention such as ATG or bone marrow transplant. The data for success is particularly strong for the age group of our three patients. Their fate, as well as others like them, is sealed. As clinicians, we look longingly to innovative research that may unravel this puzzle for effective prevention.

Conclusion

In this international enlightened era, one can only hope that the scientific community will be stimulated and challenged enough to undertake research on etiology of aplastic anemia, which might lead to more successful therapy or prevention. Lack of resources precluded use of reasonably successful ATG or BMT in our young aplastic anemia patients; the cure of which is imperative to make them productive global citizens.

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