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Case Report

Megaloblastic anemia in a teenage patient

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Introduction

Retinal hemorrhages are usually seen in diabetic and/or hypertensive retinopathy, trauma, bleeding diathesis and with an increased intracranial pressure.¹ Retinopathy due to megaloblastic anemia though rare, has been reported previously in literature.² However Roth spots, in a case of megaloblastic anemia is considered very rare indeed.^{3–5} Finally subhyaloid hemorrhage, due to megaloblastic anemia is so rare that to the best of our knowledge it has been reported of only once earlier in literature.⁶

Here we describe an interesting case of a child who was referred to this department with complains of diminution of vision in his right eye. When evaluated, multiple large white centered subhyaloid retinal hemorrhages were seen in both his eyes. The child gave a history of having initially presented with high grade fever, for which he was thoroughly investigated and accurately diagnosed as a case of megaloblastic anemia due to vitamin B 12 deficiency. He was appropriately managed with packed RBC transfusion and injection hydroxycobalamine, following which the patient became a-febrile. Childhood vitamin B 12 deficiency itself is extremely rare,⁷ and so is megaloblastic anemia as the sole cause of pyrexia.⁸ Subsequently at the time of his discharge, he noticed a decreased vision in his right eye and was referred to us. The patient was managed conservatively and followed up with regular vision testing as well as retinal examinations. The retinal hemorrhages gradually resolved, and the patient was discharged with a normal vision in both his eyes.

Case report

A 15 year old male patient, diagnosed with megaloblastic anemia was referred to the eye department, 4 days after his hospital admission, with complains of diminution of vision (DOV) in his right eye. Ocular examination revealed his best corrected visual acuity (BCVA) reduced to 6/60 in the right eye.

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The rest of the anterior segment, including the intraocular pressure (IOP) was normal i.e. 14 mm of hg as measured by the non contact tonometer (NCT). However a dilated funduscopy revealed multiple, large, white centered subhyaloid retinal hemorrhages involving the macula [Fig. 1a]. The left eye examination revealed a normal vision of 6/6 (unaided). The anterior segment and the IOP (15 mm of hg NCT) too were normal. Fundoscopy revealed Roth's spots, similar to those in the right eye; however in the left eye the macula was not involved [Fig. 1b]. A detailed history revealed that the patient had been admitted with a history of fever of 5 days duration. He also had a history of generalized weakness and dyspnea on exertion for the past 2 months. Other than the patient being a strict vegetarian there was no other positive family or personal history. Physical examination on his presentation to the hospital had revealed a temperature of 101.2° F, pulse rate 100/minute, respiratory rate 28/minute, gross pallor and mild splenomegaly. There was no cyanosis, icterus or lymphadenopathy. The patient was investigated thoroughly to evaluate the cause of the severe pallor and fever [Table 1]. The patient's hemoglobin was 4.3 gm/dl. The other positive findings were the low serum iron and serum B12 levels i.e. 45.4 µg/dl and

<83.0 pg/dl respectively, while the serum folic acid levels were normal (11.00 ng/ml). The peripheral blood smear (PBS) revealed abnormalities in the morphology of RBCs i.e. anisocytosis, poikilocytosis, macrocytes, macroovalocytes and basophilic stippling with occasional NRBC's. Bone marrow aspiration study revealed erythroid hyperplasia with megaloblastic changes suggestive of dimorphic anemia predominantly megaloblastic anemia. A provisional diagnosis of megaloblastic anemia was made and the patient was managed with packed RBC's, 3 units, over a period of 3 days. Simultaneously he was also started on injection hydroxycobalamine 1 mg, intramuscularly, daily for the next 7 days. Within 24 h of starting the above treatment the patient had become a febrile. His hemoglobin too had gradually increased to 9.1 gm/dl over the next 72 h. It was at this stage that he had noticed a DOV in his right eye and was referred for an ophthalmological review. Optical coherence tomography (OCT) done subsequently, confirmed the above mentioned fundus findings [Fig. 2a and b]. The patient was started on topical non steroidal anti inflammatory (NSAID) eye drops and was followed up on a regular basis. The hemorrhages gradually resolved [Fig. 3] and simultaneously the patient's vision too slowly improved. He was finally discharged 2 weeks after admission with a normal vision of 6/6 in both eyes and a blood

Fig. 1 – (a) Fundus photograph of the right eye. Note the subhyaloid hemorrhage overlying over the macula. (b) Fundus photograph of the left eye. Note the multiple subhyaloid hemorrhages. However the macula is spared.

Table 1 – Investigations carried out to diagnose the cause of anemia and fever.

S. No	Investigations	Report
1.	Hemoglobin	4.3 gm/dl
2.	Platelet count	175,000
3.	Total leukocyte count	$6 \times 10^9/\text{Liter}$
4.	Differential leukocyte count	
	Polymorphs	42
	Monocytes	02
	Leucocytes	57
	Eosinophils	03
5.	MCV	114.8
	MCH	37.4
	MCHS	32.6
6.	Reticulocytes	1–2%
7.	Serum folic acid	11 ng/ml
8.	PCV	13%
9.	Serum bilirubin	1.0
10.	Serum amylase	60 U/L
11.	Serum albumin	4 gm/dl
12.	Widal test	–ve
13.	Thyroid test	
	T3	0.72 ng/ml
	T4	7.22 µg %
	TSH	0.9983 micro IU/ml
14.	Osmotic fragility test	WNL
15.	HBs Ag	–ve
16.	Sickling test	–ve
17.	Stool for occult blood	–ve
18.	AST	21 U/L
19.	ALT	26 U/L
20.	Dengue serology	–ve
21.	HIV	–ve
22.	Blood for malaria parasite	–ve
23.	G ₆ PD	18.95 U/G.HB
24.	RFT	WNL

Fig. 2 – (a) OCT and Fundus photograph of the right eye. Note the hemorrhage overlying over the macula. (b) OCT and Fundus photograph of the left eye. Note the multiple large retinal hemorrhages; however none of them are involving the macula.

hemoglobin level of 11 gm/dl, after being suitably advised about the necessary dietary modifications. He was subsequently regularly followed up on an outpatient basis. Fundus photographs taken 2 months later revealed the hemorrhages totally resolved in both his eyes [Fig. 4a and b].

Discussion

This patient a diagnosed case of megaloblastic anemia, had reported to us for the first time with DOV in his right eye, which when evaluated had revealed multiple, large, sub-hyaloid Roth spots in both eyes, with involvement of the macula in only the right eye. Roth spots are white-centered

retinal hemorrhages and have been traditionally thought to be pathognomonic for subacute bacterial endocarditis. However, they have also been described earlier in association with other conditions like with leukemia, anoxia, hypertensive retinopathy, diabetic retinopathy, intracranial hemorrhage, prolonged intubation, neonatal birth trauma, complicated delivery and battered children.⁹ But Roth spots associated with megaloblastic anemia has been rarely described earlier in literature.^{3,4} The exact pathophysiology of Roths spots is still not exactly clear however it has been proposed that the mechanism involved is capillary rupture and repair.³

Megaloblastic anemias are a group of disorders characterized by peripheral blood cytopenia(s) due to ineffective hematopoiesis in the bone marrow. They are usually caused by

Fig. 3 – Fundus photograph (right eye) at the time of discharge. Note that even though hemorrhages still present, but the one involving the macula has resolved.

nutritional deficiencies of either vitamin B 12/folic acid; or both, inherited disorders of DNA synthesis, or following certain drug therapy.¹⁰

Vegetarian diets are subclassified into lactovegetarian, (diet includes only dairy products), ovovegetarian (diet includes only eggs) and lactoovovegetarian (diet includes both dairy products as well as eggs). Vegan diets are those which exclude all animal products. Human species does not synthesize vitamin B12, and therefore the exogenous intake occurs through ingestion of animal products (fish, meat and dairy products).¹¹ Several studies have also shown a reduced mean vitamin B 12 status in vegetarians, particularly among vegans.¹² The initial symptoms of vitamin B 12 deficiency are usually nonspecific i.e. unusual fatigue, appetite loss, digestion problems, nausea, anxiety, mild depression, numbness, tingling in the hands and feet, impaired memory and frequent upper respiratory infections. However its most obvious clinical manifestations are hematologic symptoms (megaloblastic anemia, pernicious anemia) and neurologic symptoms.¹³

Our patient had reported with fever of a short duration and it resolved soon after the initiation of treatment with injection hydroxycobalamine. Deficiency of vitamin B 12, as a cause of pyrexia, has been seldom reported in literature. However, megaloblastic anemia, solely as the cause of pyrexia, is indeed very rare.¹⁰

The presence of severe pallor prompted an urgent initiation of a battery of investigations to find out its exact etiology. The PBS and bone marrow findings, augmented by a low serum iron and vitamin B12 levels confirmed the diagnosis of megaloblastic anemia due to vitamin B12 deficiency.

Vitamin B 12 is the only vitamin that is synthesized exclusively by microorganisms. Dietary sources are primarily of animal origin, including meats, dairy products, and eggs. Dietary vitamin B12 deficiency is a severe problem in the Indian subcontinent, Mexico, Central and South America, as well as certain areas in Africa,¹⁴ and megaloblastic anemia

Fig. 4 – (a) Fundus photographs (right eye). Note that all the hemorrhages have got resolved. (b) Fundus photographs (left eye). Note that all the haemorrhages have got resolved.

due to Vitamin B 12 or folate deficiency is the most common cause of macrocytic anemia.

Once the patient was started on vitamin B12 therapy he showed a remarkable improvement as far as his fever as well as his hemoglobin was concerned. The retinal hemorrhages too reduced, post therapy, to finally completely disappear within a month.

Though several studies have shown that well-planned vegan and vegetarian diets are appropriate for all stages of the life cycle and rather this diet also provides a number of nutritional benefits. However, it has also been advised that the use of fortified foods or supplements can be helpful in meeting the dietary recommendations especially in diets that completely exclude animal products i.e. vegans.

Due to these health concerns, our patient, as well as his parents, on discharge, were advised to carefully plan their diet, and if necessary, even monitor his plasma vitamin B 12 on a regular basis so as to facilitate the early detection of low cobalamin status. He was also advised to include vitamin B 12–fortified foods in his diet or take vitamin B 12 supplements if necessary.¹²

Conclusion

Studies from the developed countries have shown that megaloblastic anemia's in childhood are both very rare as well as difficult to diagnose.⁷ In these cases timely diagnosis, treatment as well as its preventive aspects are of utmost importance in their management.

However vitamin B12 deficiency is not uncommon in India and is a major factor leading to megaloblastic anemia. Inadequate dietary intake, over-cooking of our food and poor absorption have been suggested as the main contributing factors responsible for the high prevalence of vitamin B12 deficiency in the Asian population.¹⁵

Vegetarian and/or vegan diets specially predispose to Vitamin B 12 deficiency and all such individuals should be advised about proper diet modifications.

Since its prevalence is relatively high in our population we also recommend that all patients presenting with pyrexia and cytopenia should be carefully evaluated for possible vitamin B₁₂ and/or folate deficiency. This in turn will go a long way in preventing the unnecessary and excessive use of antibiotics.¹⁰

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