

PERNICIOUS ANEMIA IN YOUNG: A CASE REPORT WITH REVIEW OF LITERATURE

Behera PK¹, Tripathy KP², Panigrahi R³, Tripathy S⁴

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Author details: ¹Associate Professor, ^{2,4}Professor, Department of Medicine, Kalinga Institute of Medical Sciences (KIMS), Bhubaneswar, India
³Associate professor, Dept. of Pathology, Kalinga Institute of Medical Sciences (KIMS), Bhubaneswar, India

Corresponding author: Behera PK
Associate Professor, Department of Medicine, Kalinga Institute of Medical Sciences, Bhubaneswar, India
Email: drpradip76@gmail.com

ABSTRACT

Pernicious anemia (PA) is characterized by Vitamin B12 deficiency which arises due to lack of intrinsic factor as a result of autoimmune destruction of gastric body mucosa and loss of gastric parietal cells. Generally it is considered as a disease of the elderly as its prevalence is 0.1% in general population and 1.9% in subjects over the age of 60 years. Pernicious anemia in age group below 30 years is less common (<4%). Clinical presentation of Pernicious anemia is insidious and varied ranging from subtle anemia to serious neurological manifestations with a future risk of developing neoplastic changes in stomach. It is considered as a "great pretender" because of its wide spectrum of clinical manifestations. But once diagnosed treatment is easy with parenteral replacement and maintenance of cobalamin.

Keywords: *Pernicious anemia, Atrophic gastritis, Intrinsic factor, Megaloblastic anemia, Vitamin B₁₂*

INTRODUCTION

Pernicious Anemia is an autoimmune atrophic gastritis that causes a deficiency in Vitamin B12 due to its malabsorption.^[1] Vitamin B12 malabsorption is the result of deficiency of intrinsic factor, a protein that promotes its transport to the terminal ileum for absorption.^[2] The term pernicious anemia is sometimes used as synonym for cobalamin deficiency or for macrocytic anemia but to avoid ambiguity, PA should be reserved for conditions that result from impaired secretion of intrinsic factor and atrophy of oxyntic mucosa. The first clinical description of pernicious anemia, has been attributed to Thomas Addison, in 1849.^[3] Michel Anton Biermer noticed the particular characteristics of anemia and coined the term progressive pernicious anemia.^[4] Pernicious anemia represent 20-50% of the causes of vit-B12 deficiency in adults. Given its polymorphism and broad spectrum of clinical manifestations pernicious anemia is a great pretender. Its diagnosis must therefore be evoked and considered in the presence of neurological and hematological manifestations of undermined origin. However differential diagnosis may sometimes be challenging due to the limit of available diagnostic tools. Pernicious anemia is a common disease in North Europeans but occurs in all countries and ethnic groups. The peak age of onset is 60 years with only <10% being less than 40 years of age.^[5] Here we report the case of a young man of 29 years who presented with sub acute onset paraparesis and anemia and was finally was diagnosed as a case of pernicious anemia.

CASE REPORT

A 30 years young man working as security guard in a private college from rural Odisha, India presented to us

with weakness of lower limbs, unsteadiness and clumsiness while walking with frequent falls for 3 months period. There was associated numbness and tingling sensation over hand and feet but bowel and bladder function was normal. There was no history suggestive of radicular pain, trauma, neck pain, fever or seizure disorder. There was no similar illness in past. He was a non-diabetic, non hypertensive, non smoker and nonalcoholic. He was from low socioeconomic status, married with one child and there was no history of extramarital sexual contact. He was on mixed Indian diet. The whole illness was progressing inspite of local treatment with oral medications.

On examination he was of average body built and nutritional status. Pulse was 76/min, regular. Blood pressure 110/70 mm/ Hg , There was pallor but no icterus, cyanosis, clubbing or lymphadenopathy. Jugular venous pressure not raised and there was no pedal edema. Hyperpigmentation noted over knuckles and distal phalanx in both hands (Fig. 1) and feet. There was no thyroid abnormality on clinical examination. CNS examination revealed normal higher functions. Cranial nerves examination including fundoscopy was normal. On examination of motor system there was grade 4/5 power in both lower limbs with loss of all deep tendon jerks (Bilateral knee jerk and ankle jerk). In both upper limbs power was normal but deep tendon jerks (Biceps, Triceps and Supinator jerks) were diminished. Bilaterally plantar reflex was extensor. There were no cerebellar signs but gait was ataxic and wide-based with Romberg's positive. Sensory examination revealed loss of fine touch, vibration and joint position below knee in lower limb and below elbow in upper limb. Pain and temperature sensation was intact in all dermatomes.

There was no abnormality on examination of peripheral nerves, skull or spine. Meningeal signs were absent. Examination of respiratory and cardiovascular system revealed no abnormal findings. Gastro-intestinal system and abdomen examination revealed only glossitis. With the above clinical history and examination findings, diagnosis of Vitamin B12 deficiency was considered with possible differential diagnosis of Tabes dorsalis, Freidrichs ataxia, HIV Myelopathy and Multiple Sclerosis and accordingly investigation was planned.

Routine haematological investigation revealed Haemoglobin-9.1 gm%, Mean corpuscular volume (MCV) was 121.6 fl,PCV-24.2%, ESR-15 mm, Total leucocyte count(TLC)-4,200/cml with a normal differentia count, Total platelet count(TPC)-2 lacs/cml. High MCV(>120) was in favour of a megaloblastic anemia and comment on peripheral blood smear was planned which showed presence of hypersegmented neutrophils (Fig 2),macro-ovalocytes (Fig. 3), moderate anisocytosis and poikilocytosis, presence of tear drop cells and cabot rings in Erythrocytes (Fig 4).

Among routine biochemical tests, Fasting plasma sugar was 105mg/dl, Liver function test-Total billirubin 2.4mg/dl, Direct Billirubin 0.8 mg/dl, Liver enzymes within normal level, Thyroid function test –within normal range, Serum Vitamin B12 -192pg/ml(200-835 pg/ml), Serum Folic acid 10.2 g/L(1.4-15.4 g/L),and CPK- was 34(13-60). HIV Test and VDRL Test were negative.



Fig 1: Photograph of hand of the patient showing hyperpigmentation of knuckle and distal phalanges.

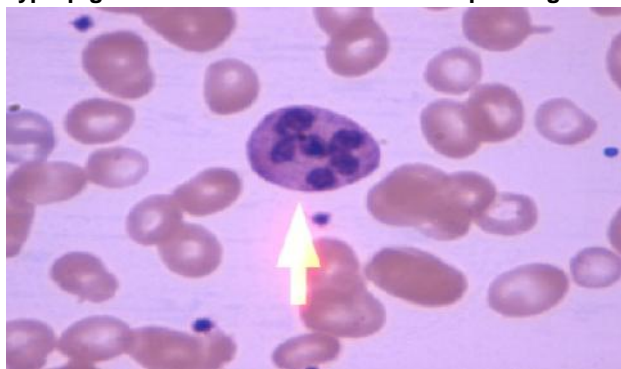


Fig. 2 Peripheral smear showing hypersegmented (6 lobed) neutrophil.(arrow)

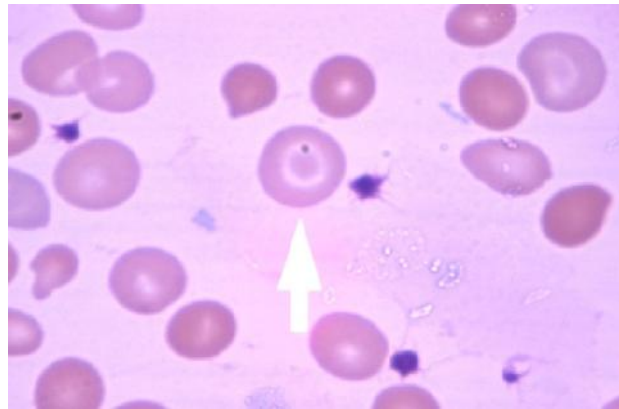


Fig 3: Peripheral smear showing a macro-ovalocyte. (arrow)

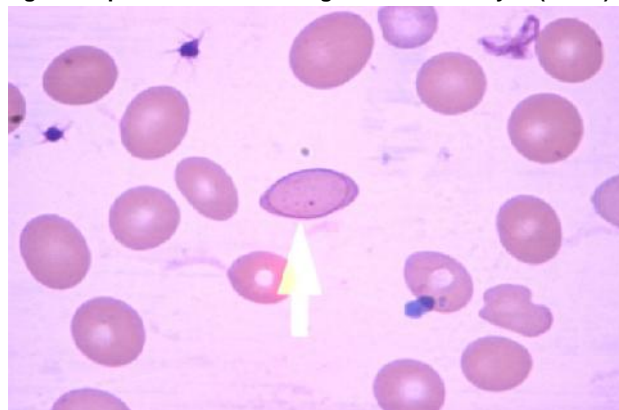


Fig 4: Peripheral smear showing a RBC with cabot ring. (arrow)

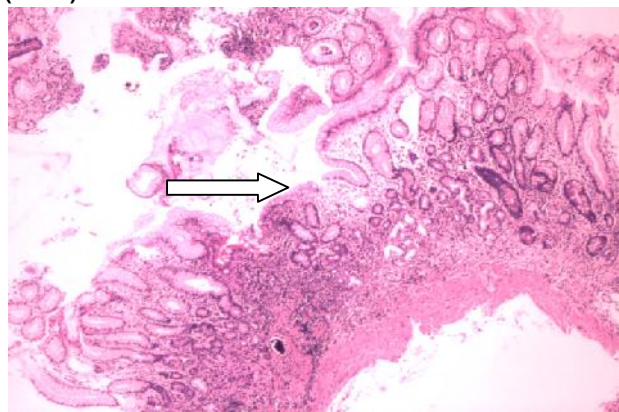


Fig 5: Gastric biopsy showing gastric atrophy.(arrow)

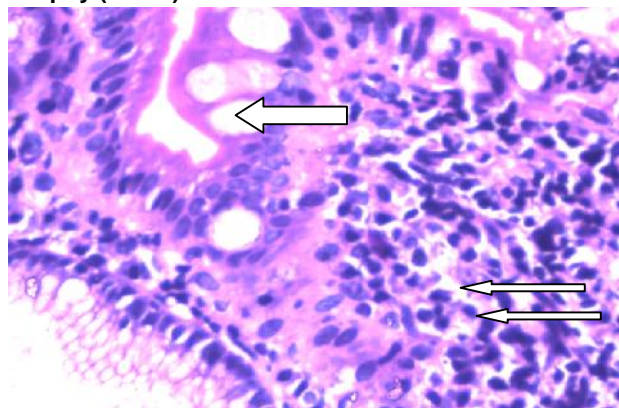


Fig 6: Gastric biopsy showing intestinal metaplasia(presence of goblet cells- single arrow mark) and plasmalymphocytoid infiltration in lamina propria(double arrow)

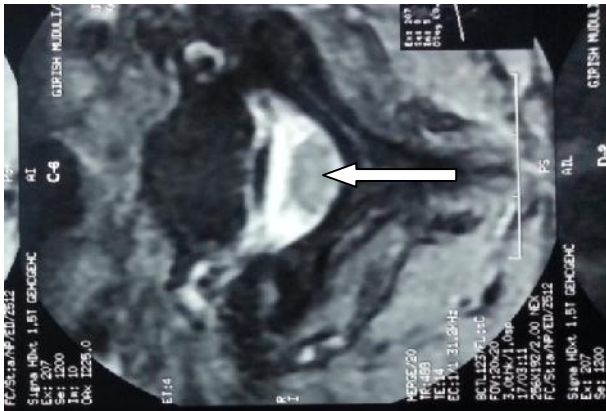


Fig 7: MRI of the Spine showing hyperintense signals in dorsal column of spinal cord.(arrow)

At this stage of investigation, subnormal serum Vitamin B12 level and megaloblastic peripheral blood picture was proved which corroborates with the clinical findings. To establish the etiology of vitamin B12 deficiency, serum Anti –Intrinsic factor antibody was done which was positive. Biopsy from gastric body showed loss of glandular epithelium (Fig. 5), intestinal metaplasia and infiltration of plasma cells and lymphocytes to the lamina propria (Fig. 6) and even into the glands confirming Pernicious anemia as the cause of vitamin B12 deficiency. MRI of the spine was done to assess the spinal cord involvement as well as to exclude any compressive lesion which showed presence of hyper intense signals in dorsal column (Fig. 7) in cervical region and confirmed absence of any spinal cord compression. Finally the case was diagnosed as a case of pernicious anemia with sub acute combined degeneration of cord and treatment was started with daily intramuscular injection of 1000 g of methylcobalamin for 1 week followed by the same dose once weekly for one month. Patient was discharged with advice to take the same dose once every month for rest of the life and followup every 6 month interval. There was almost complete recovery of all the symptoms.

DISCUSSION

Pernicious anemia (PA) also known as Biermers disease or Addisonian anemia is a macrocytic anemia due to vitamin B12 (cobalamin) deficiency, which in turn is the result of deficiency of intrinsic factor, a protein that binds avidly to dietary vitamin B12 and promotes its transport to the terminal ileum for absorption.^[6]

The deficiency of intrinsic factor is due to the presence of atrophic body gastritis which results in the destruction of oxyntic mucosa leading to loss of parietal cells which normally produces hydrochloric acid and intrinsic factor. According to literature Pernicious anemia is thought to be common among individuals of Scandinavian, English or Irish ancestry whereas it appears to be much less common in Caucasians of Italian or Greek origin.^[7] The western data suggests the prevalence of PA in general population is 0.1% and in subjects over the age 60 years it reaches 1.9%^[8] Indian data regarding the prevalence of pernicious anemia is lacking. But unlike earlier perception vitamin B12 deficiency causing megaloblastic

anemia is more common than folate deficiency^[9] But etiology of vitamin B12 deficiency was not studied in these cases. In a prospective study by Raina et al, to find out the prevalence of pernicious anemia among voluntary consenting healthy adults none of the subjects showed a positive result for anti-Intrinsic factor antibody showing PA is less common in India.^[10] Dietary insufficiency rather than PA is the predominant cause of Vit B12 deficiency in Indian population as most Indian diet is poor in Vita B12.^[11] A female predominance ranging from 1.7 to 2.0 :1 has been reported in white subjects and has been confirmed in more recent studies.^[12]

Pernicious anemia is frequently described as a disease of elderly (60 years). In one study 50% of cases were <60 years of age in particular 4% of cases were <30 years of age and 10% of cases were 30-40 years.^[2] Our patient is of 29 years which confirms that PA can occur in <30 yrs though uncommon.

Pernicious anemia is the end stage of atrophic body gastritis and is generally considered as an autoimmune disease. The autoimmune origin of PA is based on the presence of parietal cell and/or intrinsic factor autoantibodies and the frequent association of PA with other autoimmune diseases such as autoimmune thyroid disease, Type 1 diabetes and vitiligo.^[8] Atrophic body gastritis is considered a separate entity from H. pylori related atrophic gastritis because of the prevalence of H. pylori infection in severe atrophic body gastritis and pernicious anemia has been found to be low. But the potential role of H. pylori in the pathogenesis of autoimmune gastritis and PA has been explored in recent years.^[13] These studies are mostly based on the presence of Anti-GPC antibodies in individuals who are infected with H. pylori. Molecular mimicry as a basic mechanism for the initiation of gastric autoimmunity by H. Pylori has been proposed^[14] and H+/K+ATPase has been identified as the major auto-antigen.^[15]

The clinical presentation of pernicious anemia is insidious. Early symptoms may be nonspecific and related to presence of anemia per se such as weakness, asthenia, decreased mental concentration, headache and especially in elderly cardiological symptoms such as palpitations and chest pain.^[2] Other commonly reported hematological manifestations are neutropenia, thrombocytopenia or pancytopenia. Intramedullary hemolytic component due to ineffective erythropoiesis, and pseudothrombotic microangiopathy has also been reported.^[16] The most frequent signs on peripheral blood smear are the presence of macro ovalocytes and hypersegmented neutrophils.^[17]

Nervous system manifestations are common and may be the presenting feature. There is no definite relationship between the degree of anemia and the presence of neurological manifestations. In about 30% of cases neurological manifestations may be without anemia.^[18] Neurological symptoms and signs usually generate a clinical picture of combined sclerosis of the spinal cord and predominate in the lower limb. There may be weakness of limbs, clumsiness and incoordination while walking and parasthesia of limbs. Cerebral symptoms like cognitive impairment and neuropsychiatric

disorders like mood disorders, confusion, slowed mentation, delirium, panic attacks with and without phobia, hallucinations, delusion, psychosis, cataplexy and insomnia has been reported.^[19] Retrobulbar neuritis and autonomic dysfunction also occur though less common.^[20] MRI of the spinal cord shows high intensity signals in T2 weighted images most often in cervical and thoracic cord.^[21] Similar lesions can be seen in brain images also^[20]. Nerve conduction studies show abnormal peroneal and Sural nerve conduction and abnormality in tibial somatosensory evoked potential.^[22] Gastrointestinal symptoms like anorexia, dyspepsia, diarrhoea are common. Glossitis, cheilitis and aphthous ulcers are also frequent clinical findings. Majority of patients (>70%) with pernicious anemia are associated with severe gastric body atrophy with intestinal metaplasia. In about 50% of cases of pernicious anemia the gastric antrum is involved and in 27% of cases antral atrophic gastritis has been observed.^[2]

Though Schilling test and demonstration of lack of Intrinsic factor by study of gastric juice are gold standard for diagnosis of pernicious anemia^[23], they are not of practical help to the clinicians. Other criteria commonly used to diagnose PA may vary in sensitivity and specificity and include

-The presence of serum anti -IF antibodies for which sensitivity is only 50%

-The presence of histological lesions of autoimmune fundic gastritis, in the absence of H. pylori (in collected samples)

-Hypergastrinemia or increased serum chromogranin A in response to achlorhydria, which strongly points to PA in absence of proton pump inhibitor use.

Although PA is a benign disorder, it is epidemiologically and biologically linked to the development of intestinal type gastric carcinoma and gastric carcinoid Type I. In the literature the reported annual incidence of gastric cancer in PA ranges from 0.1% to 0.5%.^[24]

Treatment of vitamin B12 deficiency with PA is based on parenteral Vitamin B12 administered intramuscularly under the form of cyanocobalamin, hydroxycobalamin or methylcobalamin. The therapeutic recommendations for PA with regard to dosage and frequency of administration of vitamin B12 are divergent. In United States, France and also in India cobalamin therapy involves acute treatment at a dose of 1000 µg daily for 1 week, followed by 1000 µg per week for 1 month, then a monthly dose of 1000 µg for life.^[1,2] The dose of orally administered cobalamin greatly exceeds those required physiologically ranging from 1000-2000 µg/day.^[2]

PA patients should be monitored at least yearly by complete blood count, serum cobalamin and ferritin levels to assess adequacy of the replacement treatment and to detect early eventual onset of iron deficiency. Finally PA patients should be monitored by at least a yearly clinical interview to verify the onset of new symptoms those are suspicious of long term consequences of PA, which require immediate gastroscopic investigation.^[1,2]

CONCLUSION

PA is an often silent and under-diagnosed autoimmune disease, because its onset and progression are very slow and patients may become used to their complaints. But the clinical consequences of undiagnosed PA may be serious including irreversible neurological damage with crippling or gastric neoplastic lesions. Indian research related to pernicious anemia and epidemiological data are scanty. In contrast to the western data of common age of presentation being more than 60 years, our case was young and of 29 years. So more study (both epidemiological as well as experimental) are required from Indian researchers regarding PA for better understanding and management of this disease in Indian context.

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Conflict of Interest: The authors declare no conflict of interest while preparing this case report.

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