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Pseudo Iron Deficiency Anemia: Diagnostic Significance

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Intelligent appraisal of anemia requires evaluation of red cell hemoglobin content. This may be performed by direct observation of the blood smear for hypochromia or calculation of the mean corpuscular hemoglobin concentration (MCHC). A decrease in the quantity of cell hemoglobin signifies most commonly in the adult, a state of iron depletion resulting from chronic blood loss, much less frequently from an absorptive defect, or most uncommonly from a dietary deficiency of iron. An even rarer type of primary iron deficiency in young males has been described.

Diagnosis and treatment of true iron deficiency anemia follows a logical sequence of investigation of possible etiologies, correction of the ultimate cause and adequate iron repletion.

Awareness that a similar type of hypochromic anemia may exist in the absence of true iron deficiency is apparently somewhat less wide-spread. A variety of conditions...

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**TABLE I**

**PSEUDO-IRON DEFICIENCY ANEMIA**

1. Thalassemia.
2. Hereditary Hypochromic Anemia.
3. Refractory Hypochromic Anemia
   Responsive to Pyridoxine, nicotinic acid, oral crude liver extract.
4. Chemical Intoxications
   Lead, benzene, fluorine, carbon monoxide.
5. Hypotransferrinemia.
6. Inflammatory-Toxic
   Chronic infection, Chronic inflammation, Malignancy, Uremia.

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**Fifth Medical Clinic.
Pseudo Iron Deficiency Anemia

may produce this so-called pseudo iron deficiency anemia and they are listed in figure one. Our principal concern is with the toxic-inflammatory group represented by chronic infectious and inflammatory disease, malignancy and chronic azotemia. Here, the anemia suggesting iron deficiency as indicated by red cell morphology and hypoferrremia is belied by the fact that there is no tissue lack of iron, in contrast to the state prevailing in true iron deficiency anemia. Knowledge of this easily obtainable information provides a quick, direct differentiation of pseudo versus true iron deficiency anemia, the practical importance of which may be illustrated by brief reference to the following cases.

CASE ONE: E. R., a 48-year old white male was first seen in November, 1957, with a history of polyarthritis for six months as well as an old history of pulmonary tuberculosis intensively treated and presumably arrested. Physical examination revealed swelling, redness and tenderness in varying combinations of multiple joints consistent with a diagnosis of rheumatoid arthritis. In addition there were pulmonary findings which clinically and by x-ray indicated pleural thickening, apical scarring, multiple areas of fibrosis with large blebs and hydropneumothorax on the left.

In addition to the hematologic data recorded in figure two, the following laboratory data were recorded: Total protein 7.4 gms., albumin 1.5 gms., gamma globulin 3.8 gms. Latex fixation positive. BUN was 15 mgs. %. Up to 40 L E cells were found in the peripheral blood on several determinations. Stool guiac tests were negative.

<table>
<thead>
<tr>
<th></th>
<th>Case 1 (E.R.)</th>
<th>Case 2 (J.M.)</th>
<th>Case 3 (E.R.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>6.0-7.5 gms</td>
<td>9.0-7 gms</td>
<td>5.0-6 gms</td>
</tr>
<tr>
<td>MCHC</td>
<td>27%</td>
<td>27%</td>
<td>27%</td>
</tr>
<tr>
<td>RBC</td>
<td>Hypo +</td>
<td>Hypo +</td>
<td>Hypo + to ++</td>
</tr>
<tr>
<td>WBC</td>
<td>12,700</td>
<td>11,000</td>
<td>4,600</td>
</tr>
<tr>
<td>Reticulocytes</td>
<td>1.4%</td>
<td>3.2%</td>
<td>—</td>
</tr>
<tr>
<td>Serum Fe</td>
<td>31 mcg. %</td>
<td>—</td>
<td>45 mcg. %</td>
</tr>
<tr>
<td>Marrow</td>
<td>++ +</td>
<td>++ +</td>
<td>+</td>
</tr>
<tr>
<td>Cellularity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythroid</td>
<td>Increased</td>
<td>Increased</td>
<td>Normal</td>
</tr>
<tr>
<td>Iron</td>
<td>+ to ++</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

399
Nixon

COURSE: Over the succeeding eighteen months, the patient's arthritis improved on medical management. During this time the hemoglobin returned to a level of 11 to 12 gms. There was, however, gradually increasing dyspnea with death resulting in April, 1959 from pulmonary insufficiency. Post mortem findings were compatible with cor pulmonale secondary to pulmonary fibrosis, rheumatoid arthritis, myositis and peripheral neuritis. No definitive evidence of systemic lupus erythematosus or gastrointestinal lesion was found. Likewise there was no evidence of active tuberculosis.

COMMENT: The initial severe hypochromic anemia suggested the possibility of a complicating gastrointestinal cancer. The determination that this was a pseudo iron deficiency on the basis of the marrow hemosiderin, materially dispelled this possibility. The subsequent concomitant improvement of the anemia with the rheumatoid arthritis adequately demonstrated the relationship of these two findings.

CASE TWO: J. M., a 54-year old factory worker entered the Henry Ford Hospital July 2, with complaints of weakness, fatigue, anorexia, alternating diarrhea and constipation plus a 36 lb. weight loss, all occurring over approximately a two month period. He had been seen and treated with digitalis by his local family physician in the preceding month. There was an old history of alcoholism as well as a possible history of acute gouty arthritis in the past. Pertinent history otherwise included nocturia once per night.

Physical examination revealed a chronically ill white male appearing older than his stated age. There was evidence of considerable weight loss, early clubbing of the fingers and palmar erythema. Blood pressure was 130/80. The heart was slightly enlarged. No murmurs were heard and intermittent trigeminy rhythm was observed. Minimal hepatosplenomegaly was present. Initial impressions included probable gastrointestinal malignancy, old Laennec's cirrhosis and probable digitalis intoxication.

Pertinent hemologic data is listed in figure two. Additional laboratory findings included slight proteinuria with increased WBC's and at times RBC's as well as hyaline, granular and occasional WBC casts in the urine. Early in the hospital course, the blood urea nitrogen was 30 mgs.%, serum uric acid 8.7 mgs.%. Complete G. I. series including upper G. I., small bowel, barium enema were negative except for diverticulosis. Proctoscopic examination was negative.

COURSE: Following the first week, the patient began to manifest temperature elevations which subsequently went to as high as 103 degrees. Blood cultures were obtained at this point which revealed streptococcus viridans. At about this same time, definite mitral and aortic valvular murmurs became manifest as well as peripheral petechiae. The patient developed severe thrombophlebitis while on antibiotic therapy and heparin was added to the therapeutic program. Increasing urea retention occurred with a terminal BUN of 177 mgs.%; in addition cardiac failure only partially responsive to therapy, added to the patient's precarious plight. Death occurred on August 18, 1960. Post mortem examination revealed endocarditis of both aortic and mitral valves as well as cerebral hemorrhage.

COMMENT: A hypochromic anemia initially was in keeping with the possibility of chronic blood loss due to a gastrointestinal neoplasm. The finding of normal marrow
Pseudo Iron Deficiency Anemia

content of hemosiderin indicated that this was a pseudo iron deficiency anemia which in turn indicated the possibility of chronic infection; positive blood cultures then substantiated this suspicion.

CASE THREE: E. J., a 19-year old colored female was admitted to Henry Ford Hospital in April, 1960, with the complaints of dizziness, faintness, anorexia and a 7 lb. loss in weight noted over the preceding two months. She had experienced a sore throat with slight fever just prior to admission. There was no history of menorrhagia or other bleeding. Physical examination revealed a young, colored female with evidence of marked pallor of the mucosae and signs of a mild upper respiratory infection. There was a grade II systolic murmur, heard best at the base of the heart. Findings were otherwise negative. Hematologic data are indicated in figure two. Additional laboratory findings included a trace to 1 plus albuminuria with a few hyaline and granular casts, 15 to 25 RBC's and 5 to 7 WBC's on microscopic examination of the urine. Hemoglobin electrophoresis revealed only A hemoglobin. Complete gastrointestinal x-ray examination was negative. BUN was 19 mgs.%, creatinine 1.3 mgs.%. Serology non-reactive. PBI 5.9 micrograms. Total protein was 12.6 gms.; albumin 3.99 gms; gamma globulin 6.5 gms. LE preparations revealed up to 17 LE cells in the peripheral blood.

COURSE: Following institution of steroid therapy the patient has improved subjectively although her anemia remains unchanged.

COMMENT: The severe anemia with hypochromia originally suggested the possibility of a chronic blood loss lesion. The disparity between the level of anemia and the degree of hypochromia as well as the normal hemosiderin content of the marrow, indicated a pseudo iron deficiency anemia. Despite the absence of more characteristic symptoms and findings, the possibility of an underlying systemic lupus erythematosus was proposed and confirmed by additional laboratory data.

DISCUSSION

Although the anemia of chronic inflammatory-toxic diseases is usually no more than moderate in degree as contrasted with the more severe anemia which may occur in true iron deficiency, the evidences of hypochromia, hypoferremia, hypercupremia and elevated erythrocyte protoporphyrin may be entirely similar in the two. The degree of anemia and the tendency to hypochromic-microcytic change in general increases with duration of the underlying disease in this pseudo iron deficiency group. Likewise, marrow findings with respect to erythropoietic hyperplasia and left shift found in the particular group of pseudo iron deficiency anemias under discussion, are not dissimilar from those seen in true iron deficiency anemia. The presence of toxic changes in granulopoiesis as well as non-specific increases in plasma cells and histiocytic elements in the former group are usually of some distinguishing aid.

Since the assessment of iron stores is crucial in the differentiation of true iron deficiency and pseudo iron deficiency anemias, examination of the marrow either microscopically for hemosiderin or chemically for total non-heme iron is of fundamental importance. That evaluation of marrow iron is the most reliable and sensitive
Nixon
diagnostic test for iron deficiency is well documented. Other procedures such as
ing iron binding capacity, iron tolerance curve, radio iron plasma clearance and red cell
uptake are less accurate and more tedious. The method of marrow examination for
hemolsiderin described by Rath and Finch has been used routinely by us and found
to be most satisfactory. Its simplicity and directness allow for an immediate conclusion
with regard to the critical question of iron sufficiency. The technique is such that it
can be mastered with little effort even by those untrained in hematologic cytology.

Although complete knowledge of the pathogenesis of pseudo iron deficiency
anemia is lacking, certain evidences from clinical and experimental observations exist
to give some insight into possible mechanisms. The anemia of infection, with changes
comparable to that seen in the human, has been studied in various animal experimental
models. The counterpart of the hypochromic anemia associated with certain human
malignancies has been produced in hamsters by the injection of cell free necrotic
material from tumors. The mechanism and effect of the hypoferremia which may be
produced by a variety of stress conditions and the implications of the adrenal in this
regard, particularly with respect to the latter's influence on the reticuloendothelial
system, have been studied in some detail. Recent evidence suggests that pseudo iron
deficiency anemia as found in infection, rheumatoid arthritis and Hodgkin's disease
results from a hypoferremia secondary to defective mobilization of iron from senescent
red blood cells, following their breakdown in reticuloendothelial cells of the liver and
spleen. The probability that more than decreased serum iron is involved is indicated
by the lack of response to continued parenteral iron administration. Moreover, data
indicating decreased rate of incorporation of intravenously injected radioiron and
marrow evidence of erythropoietic maturation arrest point to decreased marrow
function as a cause of the anemia. The best evidence would imply that the defect
lies in the insertion of iron into the porphyrin molecule. Electron microscopic studies
of erythropoiesis in hypochromic hypersideremic anemias reveal evidence of a blocking
mechanism preventing incorporation of iron into the hemoglobin molecule. This
probably occurs in the mitochondria but the nature of the absent or defective
enzyme systems remains to be elucidated.

The diagnostic significance of pseudo iron deficiency anemia presents several
aspects. First, its recognition excludes the implications of true iron deficiency and
particularly those relating to gastrointestinal diseases associated with occult, chronic
blood loss. Futile search for the types of bleeding mucosal lesions which can give rise
to a hypochromic anemia may be avoided. In addition, the mistake of ascribing the
anemia solely to any gastrointestinal lesion known to be present in the particular
case can be safeguarded.

On the positive side, the finding of pseudo iron deficiency anemia requires con-
sideration and systematic exclusion of chronic infectious and inflammatory disease,
particularly of connective tissue origin, as well as certain malignancies, notably those
of the lymphoma group. Lastly, the possibility of chronic azotemia must be ruled out.

In conclusion, it may be added that as with all dependent medical entities,
diagnostic accuracy in this type of anemia allows for a rational direction to therapy
based upon discovery and treatment of the underlying disease.

402
Pseudo Iron Deficiency Anemia

SUMMARY

The morphologic red cell and sideropenic alterations of true iron deficiency anemia may be mimicked by the anemia associated with various chronic inflammatory and neoplastic diseases as well as that found with azotemia. Toxic interference with erythropoiesis occurs in these conditions and results in the production of red cells with decreased hemoglobin content. Unlike the situation which prevails in true iron deficiency anemia, iron stores are adequate; however, some biochemical abnormality induced by the pathologic state prevents the normal incorporation of iron into the hemoglobin molecule.

The diagnostic differentiation of pseudo-iron deficiency anemia and true iron deficiency anemia is most expediently made by evaluation of the marrow iron. The simplified method of examination of unstained marrow particle smears by the method of Finch, lends itself very satisfactorily to this end.

Recognition of pseudo-iron deficiency anemia obviates futile investigations for a source of chronic blood loss. Moreover, awareness of the implications of this entity often provides a clue to the true nature of the underlying disease.

REFERENCES