Red Cell Hypoplasia, Cold Hemoglobinuria and M-Type Gamma G Serum Paraprotein and Bence Jones Proteinuria in a Patient With Lymphoproliferative Disorder

By ANANDA S. PRASAD, LAWRENCE Berman, LIBORIO TRANCHIDA AND M. DAVE POULIK

THIS REPORT illustrates a dynamic or progressive relationship between a lymphoproliferative disorder associated with hypogammaglobulinemia, and myelomatosis indicated by serum protein analysis. A middle-aged man was hospitalized for hemoglobinuria and anemia requiring multiple transfusions. Later, hypogammaglobulinemia was observed. In blood, erythrocytes were normochromic, leukocyte and platelet counts were normal or increased, and small numbers (0-6 per cent) of atypical lymphocytes were present. Marrow aspirations yielded hypocellular material, but a surgically removed specimen of marrow contained large collections of lymphocytes suggestive of lymphocytic lymphoma. Approximately one year after hypogammaglobulinemia was first noted, monoclonal gammopathy (M protein) and Bence Jones proteinuria (Kappa) were documented. Three years after the first admission the patient died of infection. At autopsy, the lymph nodes and spleen were the sites of small numbers of myeloma-like cells having lymphocytic nuclei, and the bone marrow contained numerous plasmacytoid lymphocytes of the type associated with macroglobulinemia.

CASE REPORT

A 39 year old Negro man was hospitalized in December 1963 because of progressive weakness of one month’s duration. Since 1944, he had received Dilantin® for epileptic seizures. Examination revealed moderate pallor and non-tender cervical and axillary lymph nodes of 1–2 cm. diameter, but no other abnormal physical findings.

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Fig. 1.—Cell in peripheral blood. The basophilic non-granular cytoplasm is associated with an eccentrically located nucleus containing large indistinctly demarcated blocks of chromatin. Depending on whether the nuclear or cytoplasmic features are the basis for classification, the cell could be regarded as a plasmacytoid lymphocyte or lymphocytoid plasma cell.

Fig. 2.—Atypical lymphoid cell in peripheral blood. The lymphocytic nucleus is associated with non-granular basophilic cytoplasm resembling that of myeloma cells.

Initial laboratory data. Hemoglobin was 5.9 gm. %, PCV 17%, reticulocytes 1.4%, leukocytes 6550/cu. mm., and platelets 600,000/cu. mm. Erythrocytes were normocytic normochromic. Smears revealed slight polychromasia, occasional nucleated red cells, and occasional atypical lymphocytes of plasmacytoid appearance (Figs. 1 and 2).* Direct and indirect Coombs tests were negative on repeated occasions. Two marrow aspirations yielded hypocellular material containing up to 35% lymphocytes, occasional plasmacytoid lymphocytes, and up to 5% plasma cells of ordinary appearance. There were a few large reticulum cells with deeply basophilic cytoplasm resembling that of the large plasma cells of normal marrow. These constituted less than 0.1% of the cells on the smears. Routine urinalysis was unremarkable. Chest and upper gastrointestinal x-ray surveys were non-contributory.

*For morphological description of plasmacytoid lymphocytes, see the legend for Figs. 1 and 2.
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Fig. 3—Cellulose electrophoretic patterns of patient’s sera. A. Serum electrophoretic pattern in December 1963 showing normal gamma globulin level. B. Serum electrophoretic pattern in July 1964, showing hypogammaglobulinemia. C. Serum electrophoretic pattern in June 1965, showing a narrow based peak in the gamma region (M peak).

Progress and follow-up. Administration of two units of packed erythrocytes resulted in a rise of the hemoglobin to 7.8 gm. %. Four weeks after admission the patient left the hospital but he had to return two days later because of nausea, dizziness, fever, dyspnea and mental confusion. The hemoglobin was 2.2 gm. %. Plasma hemoglobin was 212 mg. % and the urine contained hemoglobin. The next day the total serum bilirubin was 2.5 mg. %, and the direct was 1.0 mg. %. Osmotic fragility of erythrocytes was normal. Ham, Stefani and Donath-Landsteiner tests were negative on repeated occasions. Cold and warm agglutinins were not detected on several determinations. Pneumonia was successfully treated with
penicillin. The transfusion of twelve units of packed erythrocytes within ten days was needed to maintain the hemoglobin between 6–7 gm %. One month after the initial admission biopsy of a cervical lymph node revealed reactive hyperplasia.

Fig. 4.—Immunoelectrophoretic analysis. A. patient’s serum; B. normal serum. Precipitin arcs developed with rabbit anti-whole human serum; C. patient serum. Precipitin arcs developed with specific rabbit anti-kappa light chains serum; D. two-dimensional zone electrophoresis analysis: a—albumin, m—myeloma globulin; E. ultracentrifugal analysis of patient’s serum: top 1:10 dil. bottom 1:12 dil. $4S_{20w}^\circ$—61%; $6.3S_{20w}^\circ$—37%; $18.9S_{20w}^\circ$—2%.

The transfusion of twelve units of packed erythrocytes within ten days was needed to maintain the hemoglobin between 6–7 gm %. One month after the initial admission biopsy of a cervical lymph node revealed reactive hyperplasia.
Subsequently there were two other episodes of hemoglobinuria, one ten months and the other two years after the first admission. All three episodes occurred after the patient left the hospital during cold weather. Four attacks of pneumonia occurred in the course of his illness, the last one just prior to his death. During these attacks the leukocyte responses were good (20,000–36,000 WBC/cu. mm. with neutrophilia and left shift) and, except for the final episode, antibiotic therapy was effective.

**Serum protein studies.** Total protein was determined by the biuret method.¹ Cellulose acetate electrophoresis was performed with the Buchler apparatus.² Agar gel immunoelectrophoresis was performed by the method of Schwick.³ Rabbit antisera against normal human gamma globulin (Cohn Fr-II) were rendered specific for heavy chain determinants by absorption with isolated Fab fragment and myeloma proteins. Antisera against kappa and lambda chains (light chains) were supplied by Dr. G. Schwick (Behringwerke, Marburg, Germany). Two-dimensional zone electrophoresis of Poulik and Smithies⁴ utilized the discontinuous system of buffers⁵ for the starch gel run (second dimension). Analytical ultracentrifugal studies were performed in a Spinco Model E system⁶ with Schlieren optics. During the first admission serum protein determinations were unremarkable. However, seven months later hypogammaglobulinemia was noted (Fig. 3). Eighteen months later a narrow based peak in the gamma region became evident. The serum albumin decreased and the gamma globulin increased. At this time proteinuria (1–2 gm./day) was first noted.

Immunoelectrophoretic analysis revealed the presence of IgG and light chains in the serum (Fig. 4a). Using specific antisera to the γG heavy chains and light chains, this protein was characterized as γ₂b, kappa.γ Kappa Bence Jones protein (Fig. 4c) but no free "H" chains or Fe or Fc fragments were demonstrated in the urine. Two-dimensional zone electrophoresis and immunoelectrophoresis corroborated the agar gel immunoelectrophoretic results. Although the serum immunoglobulin seemed to penetrate the gel matrix with difficulty (Fig. 4d, m), ultracentrifugal analysis showed the presence of 7S moiety in high concentration, thus ruling out the presence of macroglobulin (Fig. 4e).

**Miscellaneous studies.** Serum iron and unsaturated iron binding capacity, serum copper, zinc and magnesium, and red blood cell zinc were determined (6–10). The results are presented in Table 1. Serum iron on repeated occasions was high and unsaturated iron binding capacity was low. Plasma Fe-59 disappearance was prolonged and red blood cell utilization in 10 days was markedly decreased. The sacral marrow failed to take up any significant amount of Fe 59, during three weeks. Reticulocyte counts in peripheral blood were never increased. Glucose 6 phosphate dehydrogenase activity in the red blood cells was measured spectrophotometrically§ and was found to be normal. Hemoglobin electrophoresis revealed normal adult hemoglobin (Hb. A) and fetal hemoglobin was less than one per cent. Plasma erythropoietin levels were markedly elevated (16 and 15 units per ml.).Ⅱ

On two more occasions, aspirated specimens of bone marrow were hypocellular. A block of bone marrow removed surgically showed hypoplasia of erythro- and myelopoietic elements, but there were nodules of tissue composed of differentiated lymphocytes. The nodules were considerably larger than normally occurring lymphocytic aggregates and the picture was considered to represent a lymphoproliferative condition, possibly lymphocytic lymphoma. No myeloma cells were seen (Figs. 5–7). The marrow biopsy was reported two months before the completed studies of the serum protein showed the presence of myeloma protein.

**Therapy.** The patient required two to three units of packed erythrocytes almost every three weeks. Altogether he received 140 transfusions throughout a three year period. Six

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¹Buchler Instruments, Inc., Fort Lee, N. J.
²Beckman Model Analytical Ultracentrifuge, Inc., Cincinnati, Ohio.
³We are grateful to Dr. H. G. Kunkel, Rockefeller Institute and Dr. J. L. Fahey at NIH for typing this protein.
⁴Kits from Calbiochem, Los Angeles, Calif., were used.
⁵We are grateful to Dr. Edward Powsner for these assays carried out on polycythemic mice.
Table 1.—Summary of Miscellaneous Laboratory Data

<table>
<thead>
<tr>
<th>Subject</th>
<th>Iron µg. %</th>
<th>Unsaturated Iron Binding Capacity µg. %</th>
<th>Copper µg. %</th>
<th>Zinc µg. %</th>
<th>Magnesium meq/L</th>
<th>RBC Zinc µg./ml</th>
<th>Plasma Fe-59 Disappearance Rate T 1/2 in min.</th>
<th>RBC Fe-59 Utilization in % in 10 days</th>
<th>RBC Survival (Cv-51) T 1/2 in days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>207–269*</td>
<td>71–114</td>
<td>100</td>
<td>75</td>
<td>1.70</td>
<td>12</td>
<td>240</td>
<td>18</td>
<td>24</td>
</tr>
<tr>
<td>Normal Values</td>
<td>87±14†</td>
<td>200±50</td>
<td>125±22</td>
<td>100±14</td>
<td>1.90±0.19</td>
<td>14±1.5</td>
<td>60–90</td>
<td>90–100</td>
<td>27–30</td>
</tr>
</tbody>
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*The ranges of several determinations on different occasions.
†Mean ± S.D.
Fig. 5.—Section of surgically removed iliac bone marrow. The marrow is diffusely infiltrated with lymphocytes, the majority of which appear as cells with darkly staining nuclei. Two poorly circumscribed foci of lymphocytes are present.

weeks after initial workup, prednisone 40 mg./day for 14 days, followed by a maintenance dose of 15 mg./day was administered for 4 weeks. Since malignant lymphoma had been considered, treatment with Cytoxan® 150 mg./day for one week followed by a maintenance dose of 50 mg./day was given for twelve weeks. At the end of this therapy, he was discharged, improved (hemoglobin 10 gm. %). However, he returned shortly thereafter for further blood transfusions; at this time, he received Delatestryl® 200 mg. three times per week (1M) for five months without any significant improvement.

In March 1966, jaundice and well-defined hepatomegaly developed. Serum transaminases were increased. Serum alkaline phosphatase was 12 B.U. It was thought that the patient had developed serum hepatitis of the cholestatic type. On July 18, 1966, the patient developed pneumonia. He was treated with Polycillin-N† 1 gm. four times a day intravenously but on July 25, 1966, he expired.

**Autopsy Findings**

Lymph nodes were enlarged in the hilar, peripheral, mediastinal and retroperitoneal areas (4 cm. in diameter). The spleen weighed 400 gm. Bronchopneumonia and pericardial effusion (400 ml.) were noted. The thymus was atrophic and fatty.

*Squibb and Sons, New York, N. Y.
†Bristol Laboratories, Syracuse, N. Y.
Fig. 6—Higher magnification of the edge of one of the lymphocytic nodules shown in figure 5. On the right, a megakaryocyte is visible, and on the left the tissue is composed mainly of differentiated lymphocytes. Occasional plasma cells, and unidentified large primitive cells with vesicular nuclei are present.

Histologic observations. There was extensive siderosis of spleen, liver, lymph nodes, pancreas, adrenal glands, kidneys and myocardium. Small amounts of hemosiderin were present in mucosal epithelial cells and submucosal macrophages of the small intestine. In the spleen, the pigment was confined to the red pulp and mainly in littoral reticulum cells; in the liver it was present in hepatic cells, Kupffer cells, and macrophages in the portal areas; in lymph nodes it was seen almost entirely in sinusoidal macrophages; in pancreas, hemosiderin deposits were very extensive in acinar cells and macrophages of connective tissue; in adrenal glands it was confined to cells of the zona glomerulosa; in kidneys it was seen in tubular epithelial cells, and in myocardium practically all muscle cells had excessive amounts of iron-staining material. In contrast to these findings, there were only occasional hemosiderin-containing macrophages in bone marrow where the amount of stainable iron did not appear greater than normal.

Cytologic Findings in Sections

Bone marrow. Except for occasional scattered microscopic foci of proliferating fibroblasts associated with atrophy of myeloid tissue, there was generalized hypercellularity, with almost complete absence of fat cells. The myeloid tissue was largely replaced by accumulations of small lymphocytes interspersed with scattered primitive cells, a few with eccen-
Fig. 7.—Imprint of lymphocytic nodule at the same magnification used for figure 6. The majority of the cells are typical micro- and mesolymphocytes. Near the center of the field a large reticular lymphocyte is present.

trically placed nuclei, and similar but smaller, more differentiated cells resembling plasmacytes. Varying admixtures with granulocytes and reduced number of erythroblasts were found among the other cells. There were no foci or collections of any single cell type and the overall histologic picture was not that of focally or diffusely scattered groups of atypical plasmacytic cells, as is usual in myelomatosis.

Spleen. The red pulp was congested, and the usual lymphocytic elements were replaced by a mixture of plasmacytoid and lymphocytoid cells similar to those seen in the bone marrow. In the spleen there were relatively fewer small lymphocytes and more of the primitive cells. The white pulp was diminished in extent and consisted mainly of irregular slender columns of small lymphocytes.

Lymph nodes. The sinusoidal architecture of the enlarged lymph nodes was preserved but follicles were diminished in size and number. The medullary cords and cortex contained atypical plasmacytoid and lymphocytoid cells of the types found in bone marrow and spleen (Fig. 8).

Prostate. In one section a distended duct containing inspissated material was surrounded by a collar of densely packed mononuclear cells in a distribution similar to that seen in chronic lymphocytic leukemia. The lesion was composed of a mixture of differentiated small plasma cells and lymphocytes of various sizes.
Fig. 8.—Section of a medullary cord of an enlarged lymph node obtained at autopsy. The smallest cells are typical microlymphocytes. Other cells with similar but eccentrically located nuclei have more cytoplasm which gives them a plasmacytoid appearance. Occasional cells of approximately the same size have dense chromatin and darkly staining cytoplasm typical of small plasma cells. In addition, the field contains scattered plasmacytoid cells with larger and more vesicular nuclei, occasionally with small nucleoli. A few of the larger cells with round nuclei and more abundant cytoplasm resemble forms often seen in sections of myeloma tissue, but the over-all pattern is that of a mixed infiltrate of various lymphocytoid and plasmacytoid cells, rather than a uniform mass of any single cell type.

Cytologic Findings in Imprints

Bone marrow. The predominating non-myeloid elements were lymphocytes and these were almost exclusively small differentiated cells. There was also an increase of typical differentiated small plasma cells similar to those seen in normal marrow. These were rare examples of less differentiated plasma cells of the types seen in lymph node and spleen imprints, described below. There were no collections of atypical plasmaicytoid cells of the type usually associated with myelomatisis.

Spleen. In addition to the normally present lymphocytes of different types, scattered band form and polymorphonuclear neutrophils and occasional eosinophil and basophil granulocytes were seen. There was an increase of reticulum cells, the majority of which contained hemosiderin. There was a great increase of differentiated typical plasma cells with coarse nuclear chromatin and eccentrically located nuclei without visible nucleoli.
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Fig. 9.—Imprint of spleen obtained at autopsy. In the lower right quadrant of the field there are two small differentiated lymphocytes, two plasmacytoid cells with lymphocytoid nuclei, and a large reticular lymphocyte. The other cells include large forms with eccentrically located nuclei having coarse chromatin patterns. In a few cells, faintly visible small nucleoli are present. These are the cells discussed in the text as occurring in microscopic foci and resembling types seen in myeloma.

There were occasional plasmacytic cells with stem cell nuclei of plasmablasts. Cells with plasmacytic cytoplasm and lymphocytic nuclei were very numerous. However, in addition, the spleen imprints contained small collections of large plasmacytoid cells with nuclei containing coarse chromatin. Also, there were similar cells with slightly less differentiated nuclear chromatin patterns and nucleoli (Fig. 9). The nucleoli were not as large as those seen in many types of myeloma cells. Nevertheless, these cells were types often seen in our cases of myelomatosis but they made up a very minor part of the cell population. The overall pattern was that of a mixture of lymphocytes, atypical plasmacytoid lymphocytes, and plasma cells.

Lymph nodes. In addition to macrophages and lymphocytes of various sizes and degrees of differentiation, there was an increase of typical plasma cells with dense chromatin and deeply basophilic cytoplasm containing juxtanuclear archoplasm. There were also numerous larger cells with similar cytoplasm and less differentiated nuclei resembling those of myeloblasts or lymphoblasts but without enlarged nucleoli. Numerous lymphocytoid plasma cells, or plasmacytoid lymphocytes (according to which morphologic feature is emphasized) were seen intimately mixed with other cells.
Discussion

Did this case represent an unusual example of multiple myeloma? Except for the changes in the serum proteins, which appeared almost eighteen months after the first admission, accompanied by Bence Jones proteinuria in moderate quantities, no other known clinical features of multiple myeloma were present. During life, at the time myeloma protein was discovered in serum, the bone marrow contained lesions resembling lymphoma of lymphocytic type, and no myeloma cells were present. At autopsy, the predominant abnormal cells in lymph nodes and spleen were atypical cells of plasmacytic and myeloma-like appearance but having lymphocytic nuclei. In the bone marrow, the atypical cells were small plasmacytoid lymphocytes. The cytologic changes were those usually associated with macroglobulinemia, but the presence of Bence Jones protein in urine and progressive increase in IgG serum protein were suggestive of multiple myeloma.

Hypoplastic anemia and intermittent hemoglobinuria in multiple myeloma have not been reported to our knowledge. During the initial period of observation, while anemia was predominant, the serum proteins were normal. Approximately seven months later hypogammaglobulinemia was noted. Slightly enlarged lymph nodes revealed only reactive hyperplasia but a biopsy of bone marrow showed a mass composed of differentiated lymphocytes, and no evidence of myeloma. About this time, reexamination of the serum showed the presence of “M” type protein. The sequence of events suggests the operation of a mechanism whereby some stimulus led to a proliferation of lymphocytic tissue, followed ultimately by the emergence of a single group or clone of neoplastic cells responsible for the monoclonal gammopathy. It is possible that given prolonged survival, the patient would have developed typical features of multiple myeloma. This view is supported by the presence of a lymphoma-like lesion in marrow during life, followed by the appearance of numerous plasmacytoid lymphocytes in bone marrow together with infiltrations in lymph nodes and spleen with myeloma-like cells with lymphocytic nuclei at autopsy.

Patients with primary acquired agammaglobulinemia have an unusual tendency to lymphoreticular neoplasia and there is a particularly frequent association of thymomas with primary acquired agammaglobulinemia. In the present case, however, the hypogammaglobulinemia was only temporary, and a thymoma was not present.

Benign monoclonal gammopathy (“M” type protein) has been noted in a small number of elderly patients who showed no evidence of multiple myeloma or macroglobulinemia even after a prolonged period of follow-up. A recent report described one such patient who developed typical multiple myeloma sixteen years after the onset of hyperproteinemia. This may mean that monoclonal gammopathy without the classical histologic manifestations of multiple myeloma may precede the clinical manifestations of multiple myeloma. Our patient exhibited light chain (Kappa) proteinuria. Bence Jones proteinuria has not been observed in patients with benign monoclonal gammopathy. Thus the present case does not fit this category.

Monoclonal gammopathy has been noted in conditions other than multiple
myeloma and macroglobulinemia. Presence of "M" protein in sera has been reported in certain carcinomas but morphologic studies in those cases were not described in sufficient detail to rule out coexistence of myeloma.

A small number of patients with malignant lymphoma show changes in serum gamma globulin fractions. These include hypogammaglobulinemia in chronic lymphocytic leukemia or macroglobulinemia in lymphoblastic lymphoma as well as Waldenström's macroglobulinemia which presents a lymphoma-like clinical picture with plasmacytoid lymphocytes being numerous in blood and bone marrow and often the predominating cells in the tissues. Monoclonal gammopathy consisting of IgG or IgM has also been described in patients with lymphocytic lymphoma or chronic lymphocytic leukemia, reticulum cell sarcoma and Hodgkin's disease. In recently described examples of "heavy chain" disease, the predominant cells were plasmacytes and lymphocytes of varying maturity. Thus there does not yet seem to be a discernible correlation of cellular morphology with the type of immunoglobulins being synthesized at the time of biopsy in such cases.

If one were to consider a related origin of both lymphocytes and plasma cells from a common precursor, multiple myeloma might belong at one extreme of a spectrum where an abnormal response results in the production of myeloma cells which are mainly responsible for increased production of IgG, IgA and/or Bence Jones proteins. The present case most likely represents the opposite extreme of the spectrum, manifesting itself at the beginning as a lymphoproliferative disorder associated with hypogammaglobulinemia in which the predominant cells of the tissue lesions are lymphocytes. The histologic findings and the changes in serum protein findings suggest that a progression from one end of the spectrum to the opposite may be expected to occur occasionally. Near the end of life of the patient, the "M" type protein in the serum belonged to the IgG Kappa type and the urinary protein was exclusively light chain (Kappa) which resembled that found in typical myeloma patient. These observations suggest that a lymphoproliferative disorder associated with hypogammaglobulinemia may, in some instances, represent a premyeloma condition.

According to the concept of the "immunoproliferative disorders" proposed by Dameshek, it was suggested that lymphoproliferative, plasmoproliferative, and reticuloproliferative types represent self-perpetuating activities of cells of the immune complex, and that a definite categorization of the exact type of proliferation may sometimes be impossible. Our patient might belong to a transitional type of lymphoproliferative disorder with some features of a plasmoproliferative disturbance.

The hyporegenerative anemia of our patient, indicated by erythroblastic hypoplasia, continuous absence of reticulocytosis and isotopic studies of iron metabolism, was associated with hypogammaglobulinemia. Although a similar association has been noted by others in a few cases, the relationship between dysimmunoglobulinemia and red cell hypoplasia remains unclear. Primary thymoma-associated aregenerative anemia was ruled out by the autopsy in our case. Dilantin® therapy is known to be associated with erythroid hypoplasia but in our case this drug was discontinued when the patient was first
seen and he did not receive any other drug known to cause erythroblastic hypoplasia for three years prior to his death. On the other hand, a role of Dilantin® in producing the initial lymphoproliferative changes cannot be ruled out.

Another unexplained feature was the intermittent hemoglobinuria. The serological tests for syphilis were negative, cold agglutinin titers were not increased except terminally, and Ham, Stefani and Donath-Landsteiner tests were negative repeatedly.

SUMMARY

This paper documents an unusual example of hypoplastic anemia, intermittent hemoglobinuria appearing in cold weather, and lymphoproliferative disease associated with hypogammaglobulinemia and repeated infections, followed by the appearance of a monoclonal gammopathy (IgG-Kappa) and Bence Jones proteinuria (Kappa), with tissue lesions more characteristic of macroglobulinemia than of multiple myeloma, in a middle-aged Negro.

SUMMARIO IN INTERLINGUA

Es reportate un caso inusuai de anemia hypoplastic, intermittente hemoglobinuria manifeste in tempore frigide, e morbo lymphoproliferative, associate con hypogammaglobulinemia e repetite infectiones, sequite per le apparition de un gammopathia monoclonal (IgG-Kappa) e proteinuria de Bence-Jones (Kappa), con lesions tissular plus characteristic de macrogloubulinemia que de myeloma multiple. Le patiente esseva un masculo de racia nigre de etate medie.

ACKNOWLEDGMENT

We acknowledge gratefully the cooperation of Dr. Joel Shrager, Chief, Department of Pathology, Veterans Administration Hospital, Dearborn, Michigan, for making the autopsy material on this case available to us. We wish to thank Mr. Virgil Schwandt and Miss Norma Sfara for their able technical assistance.

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