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Primary Macroglobulinemia:

Death due to Mesenteric Vascular Occlusion with Gas in the Portal Venous System

A. M. EDWARDS, M.D., F.R.C.P.[C],* L. B. COSTOPOULOUS, M.D.† and H. E. BELL, M.D.,‡ *Edmonton, Alta.*

ABSTRACT

Clinical features presented by a patient with primary macroglobulinemia over a four-year period included cachexia, weight loss, bleeding tendency, anemia, lymphadenopathy, hepatosplenomegaly and recurrent pulmonary bacterial infections. Immunoelectrophoresis demonstrated the presence of a β_2 macroglobulin which, on ultracentrifugation, was found to have a sedimentation constant of 14.9 $S_{20,w}$; this macroglobulin constituted over 40% of the total serum protein. Postmortem findings included the typical "naked" lymphocyte infiltration of the reticuloendothelial system, with septic embolization from a terminal Gram-negative bacteremia, associated with a mesenteric vascular occlusion. A feature of particular interest was the antemortem appearance of gas in the portal venous system, shown on two abdominal scout radiographs taken one and two hours before death. The diagnostic significance of this rare radiologic sign is discussed.

SOMMAIRE

Dans le tableau clinique d'un malade atteint, depuis quatre ans, d'une macroglobulinémie primaire, on notait: cachexie, perte de poids, tendance à l'hémorragie, anémie, lymphadénopathie, hépato-splénomégalie et infections pulmonaires récidivantes d'origine bactérienne. L'immuno-électrophorèse a permis de mettre en évidence la macroglobuline β_2 qui, étudiée par ultracentrifugation, avait une constante de sédimentation de 14.9 $S_{20,w}$ et qui constituait plus de 40% du total des protéines. Parmi les constatations post-mortem, on trouvait l'infiltration lymphocytaire typique du système réticulo-endothélial, avec embolie septique provenant d'une bactériémie terminale à Gram-négatif et accompagnée d'une occlusion des vaisseaux mésentériques. Une constatation ante-mortem présentant un intérêt particulier était la présence de gaz dans le système porte, qu'on pouvait voir sur deux films simples de l'abdomen, pris une heure et deux heures avant la mort. L'article étudie la signification diagnostique de ce signe radiologique rare.

PRIMARY macroglobulinemia is a rare condition characterized by a variable clinical picture and the presence of a large amount of a high-molecular-weight protein in the serum. Waldenström in 1944 first described the condition as an idiopathic and progressive, probably neoplastic disturbance of the reticuloendothelial system, involving the lymphoidoplasmacytic elements. It has since been recognized as being closely related to myeloma and lymphoma. It tends to run a progressive downhill course averaging 38 to 40 months in duration. It is more common in elderly men.

Physiological amounts (200-300 mg. %) of macroglobulins may be present in the serum of normal people[1] and larger amounts of macroglobulin can occur in sera of patients suffering from neoplastic or collagen diseases, nephrosis, hepatic cirrhosis and chronic infections or lymphoma. These are classed as cases of "secondary macroglobulinemia".[1, 3, 4] By definition on a biochemical basis, macroglobulinemia is said to be present when more than 5% of the total serum proteins have a sedimentation constant greater than 15 Svedberg units.[1] The molecular weight of this globulin is estimated to be about one million.

The following report describes the four-year clinical course of a patient with this disease who showed most of the clinical and biochemical characteristics reported in the 187 cases compiled from the world literature in the period 1944 to 1961.[2] Several interesting variations of the disease course are illustrated. Particularly worthy of note is the mechanism of death from mesenteric vascular occlusion associated with Gram-negative septicemia. This was accompanied by the interesting and rare antemortem radiological sign of portal venous gas.

From the Departments of Medicine, Radiology and Clinical Laboratory Services, University of Alberta Hospital and University of Alberta Medical School, Edmonton.
*Attending Staff, Internal Medicine, University of Alberta Hospital, Edmonton; Lecturer, Department of Medicine, University of Alberta Medical School.
†Chief Resident, Diagnostic Radiology, Department of Radiology, University of Alberta Hospital.
‡Assistant Professor of Pathology, University of Alberta; Assistant Director, Department of Clinical Laboratory Services, University of Alberta Hospital.

CASE REPORT

A 69-year-old white farmer was admitted to the University of Alberta Hospital in January 1962, with symptoms of four years' duration which had become

progressive. These consisted of recurrent anemia with weakness and malaise, bruising and epistaxis, lymphadenopathy noted for one year, and recurrent bouts of bacterial pneumonia.

When first seen, he was pale and listless and had generalized lymphadenopathy with firm rubbery nodes 1 to 3 cm. in diameter. There was no hepatosplenomegaly. The hemoglobin was 7.9 g. % and the blood smear showed orthochromic erythrocytes and adequate platelets. The leukocyte count was 5500 per c.mm., of which 50% were lymphocytes. The erythrocytic sedimentation rate was 47 mm./hr. The total serum protein level was 9.4 g. % with a tall β_2 peak evident on the electrophoretic record (Fig. 1). Agar electrophoresis revealed the presence of a homogeneous blob between the beta and gamma positions, contrasted to the normal electrophoretic pattern (Fig. 2).

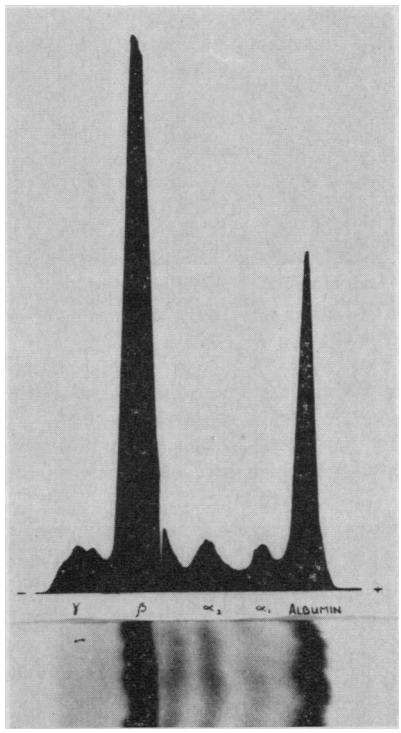

Fig. 1.—Paper electrophoresis revealing a total serum protein of 9.4 g. % with a tall β_2 peak.

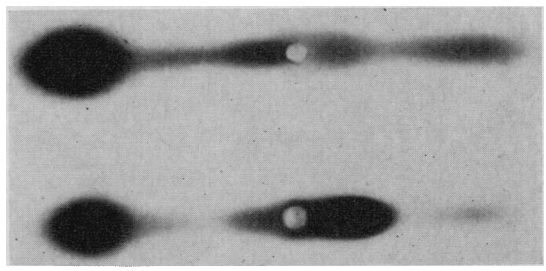

Fig. 2.—Homogeneous blob between beta and gamma positions revealed by agar electrophoresis, in contrast to the normal electrophoretic pattern.

Ultracentrifuge studies confirmed the presence of a pathological macroglobulin with a concentration of 42.7% of the total protein and with a sedimentation constant of 14.9 $S_{20,w}$* (Fig. 3). The sedimentation runs were carried out on serum diluted 10 times with 0.15 M NaCl at 59,780 r.p.m. and a bar angle of 50°.

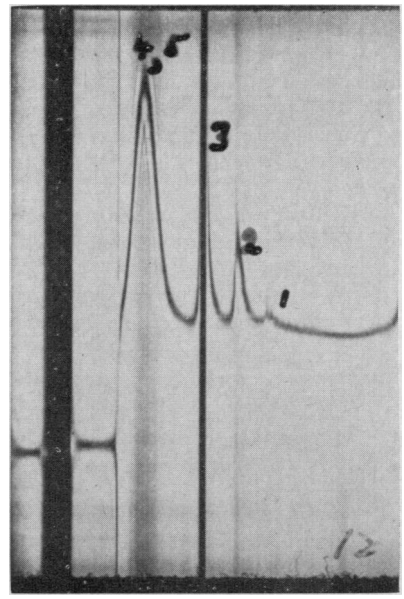

Fig. 3.—Ultracentrifugal analysis. 12 min. 59,780 r.p.m.

Component:	$S_{20,w}$ *Value*	*% Relative Amount*
1. Physiological macroglobulin	27.6	1.6
2. Physiological macroglobulin	20.9	8.9
3. Pathological macroglobulin	14.9*	42.7
4. Globulin	6.7	3.5
5. Albumin	4.2	43.3

Immunoelectrophoresis demonstrated a dark band of precipitation against β_2 macroglobulin antiserum (Fig. 4). The specific antiserum used in this study was horse antihuman γ_1M (β_2M), batch No. 501H, obtained from Behringwerke A.G. Germany. This antiserum has shown a markedly increased β_2M precipitation in six cases in which macroglobulinemia has been proved by ultracentrifugation. Incubation of serum with penicillamine in these cases has shown reactivity of anti γ_1M (β_2M) antiserum with the altered macroglobulin. No marked increase in precipitation has occurred in many other human sera tested.

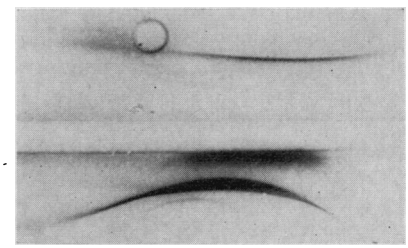

Fig. 4.—Immunoelectrophoresis: Note dark band of precipitation against β_2 macroglobulin antiserum.

The Sia water test was negative, as it was on subsequent admissions. Tests for cryoglobulins and Bence Jones proteinuria were also negative. Clotting parameters were normal, as were clot retraction tests,

*The data were corrected to standard conditions (H_2O at 20° C.).

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and fibrinolysins were absent. Coombs test, cold agglutination and quantitative gamma globulin were normal.

Marrow biopsies were negative, and cervical and inguinal node biopsies were not considered diagnostic.

The patient was transfused and discharged on prednisone, which was continued for several months during which he did not improve. The anemia recurred and necessitated transfusion. Minor bouts of pneumonia and acute suppurative appendicitis were treated by the family physician.

On readmission to the University of Alberta Hospital in February 1963, the patient was wasted and chronically ill, with a weight loss of 25 lb. over the previous year. Hepatosplenomegaly was present at that time, in addition to lymphadenopathy, anemia and pallor.

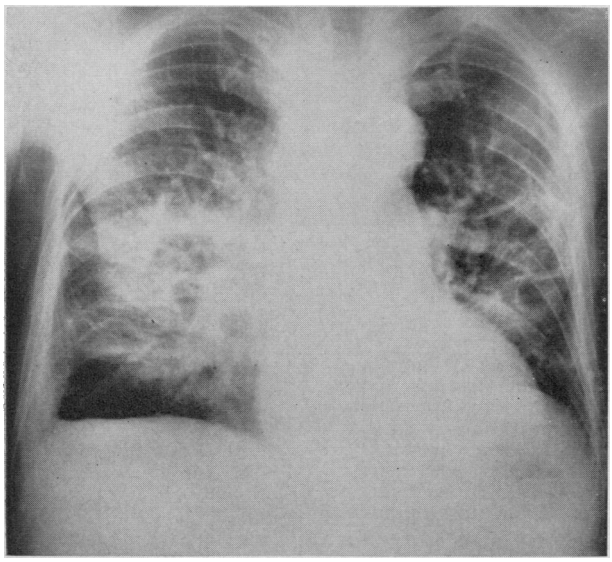

Fig. 5.—Chest radiograph showing well-marked fibrosis.

During this second admission he developed his sixth bout of bronchopneumonia. *Diplococcus pneumoniae* was grown from blood and sputum, and the patient responded fairly well to penicillin. The chest radiograph at that time showed well-marked fibrosis secondary to the repeated infections (Fig. 5).

The hemoglobin was 6.3 g. %; the leukocyte count, 6700 per c.mm., 70% of which were lymphocytes. Skeletal radiographs showed mild osteoporotic change. The patient had no bone pain at any time.

Considerable vascular sludging and segmentation were seen on retinoscopic examination, and blood viscosity studies showed a marked increase of 4.7 minutes by the Ostwald capillary viscometer (normal: 1.4-1.8 min.).

The patient was transfused and digitalized and was given fairly large daily maintenance doses of penicillin. He was also started on 8 mg. per day of chlorambucil, and discharged on 6 mg. per day as maintenance dosage; this has been reported to be an occasionally successful form of therapy for certain patients with this disease.[5, 6] He was discharged on March 16, 1963.

On March 24, 1963, he was readmitted after several days of increasing abdominal discomfort, with pain, ileus, and abdominal distension on the day before admission.

A blood culture was ordered but unfortunately was not obtained ante mortem. Treatment by means of intravenous fluids and vasopressors and attempts at abdominal decompression were of no avail.

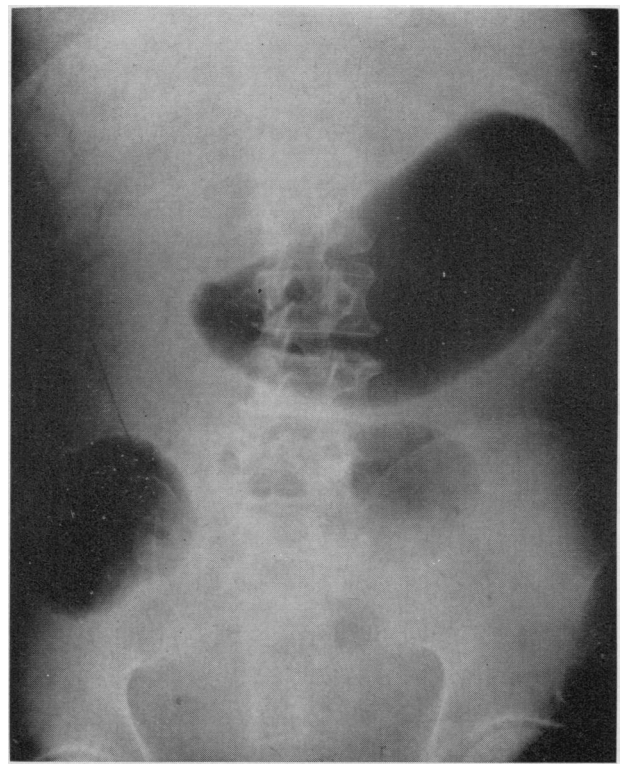

Fig. 6.—Abdominal flat plate showing portal venous gas pattern extending into small venous radicles laterally and peripherally, with accompanying distension of stomach and small bowel.

After the flat plate of the abdomen was obtained and partial decompression was accomplished, the pa-

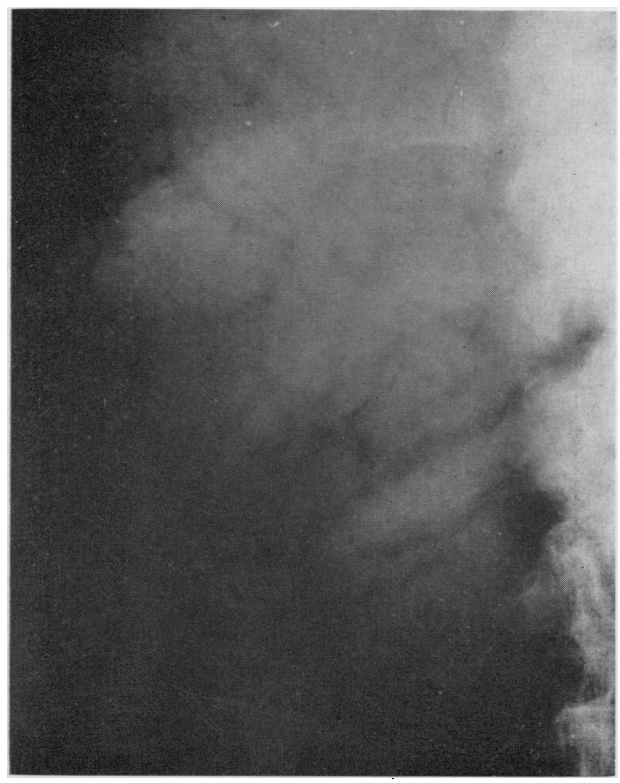

Fig. 7.—Close-up view of venous gas pattern in the right lobe of the liver.

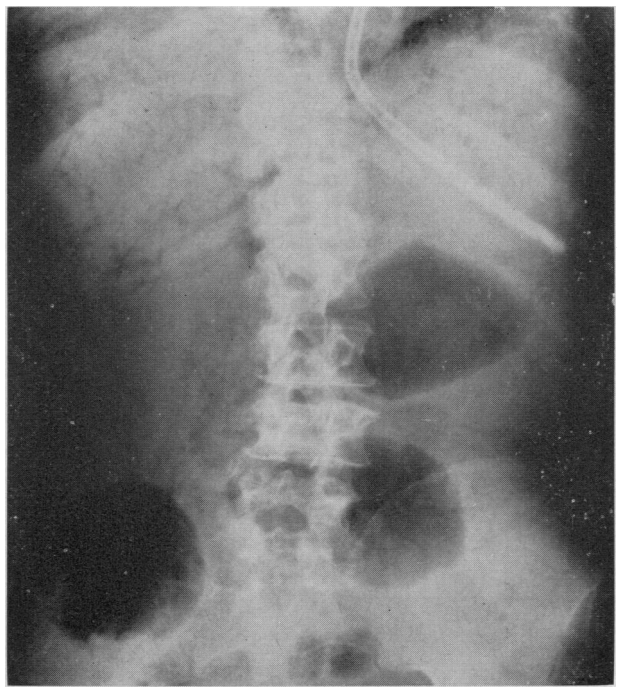

Fig. 8.—Repeat abdominal flat plate showing a more striking generalized venous gas pattern. This radiograph was taken one hour after that illustrated in Fig. 6 following gastric decompression by duodenal tube. The patient died less than one hour later.

tient went into irreversible shock and died two hours after admission.

Fig. 6 shows this patient's portal venous gas pattern extending into small venous radicles laterally and peripherally, with gastric and small-bowel distension.

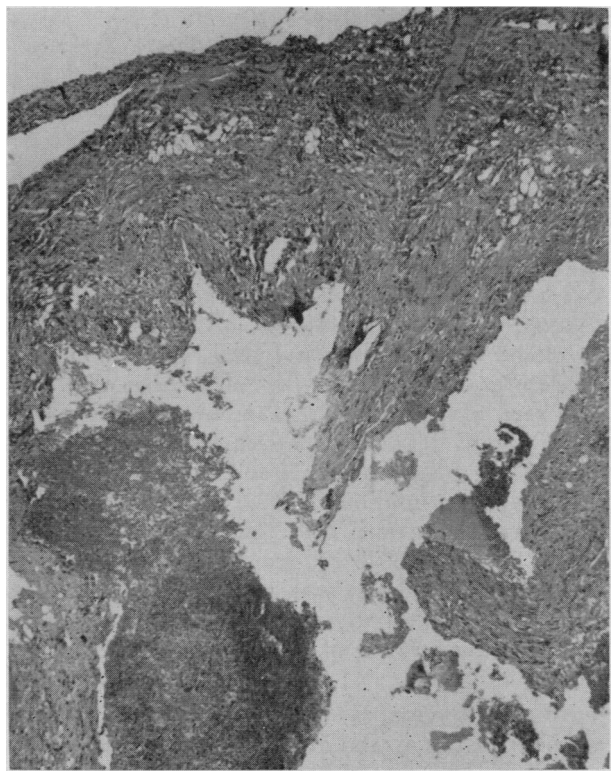

Fig. 9.—Antemortem thrombosis of superior pancreaticoduodenal artery with rupture of the wall at the site of hemorrhage into the abdominal cavity (lower right of photograph).

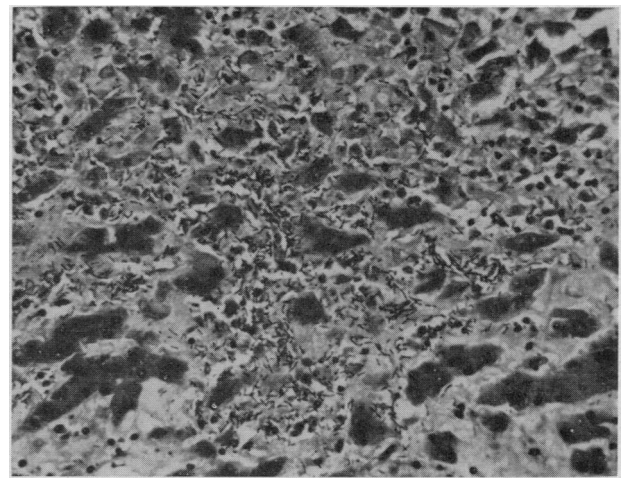

Fig. 10.—Antemortem septic necrosis of liver with numerous bacteria in areas of cellular change.

Fig. 7 presents a close-up view over the right lobe of the liver showing striking detail of the venous gas pattern.

A repeat abdominal flat plate (Fig. 8) taken one hour after the initial film, after some gastric decompression had been accomplished by means of a duodenal tube, revealed a more striking generalized venous gas pattern. This observation was made less than one hour before death.

The pre-necropsy diagnosis was mesenteric vascular occlusion with septicemia, probably caused by a gas-forming coliform organism. This was confirmed by the findings at autopsy, which was performed 14 hours after death. Postmortem cultures grew *Aerobacter*

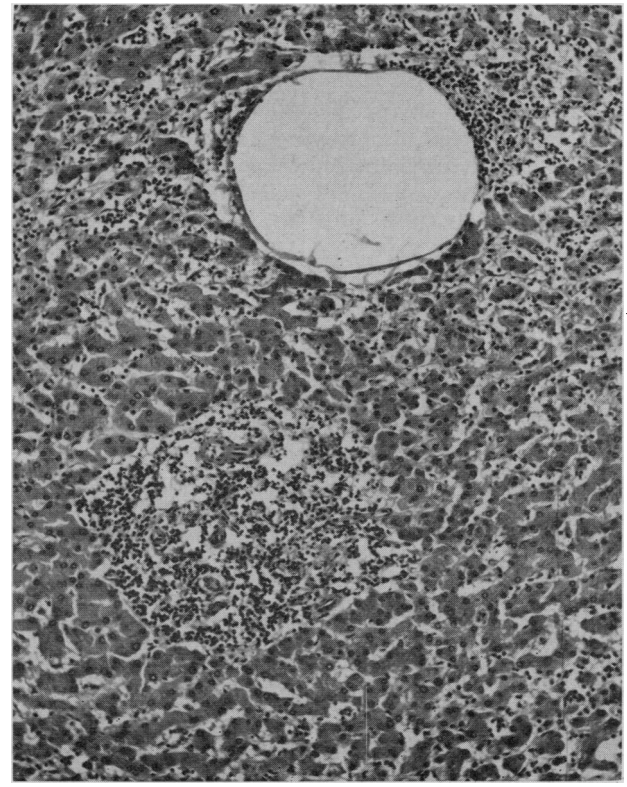

Fig. 11.—Hepatic portal infiltrate of small atypical "naked" lymphocytes of the "lymphocytoid-reticulin" type seen in macroglobulinemia. A small portal venous radicle distended by gas is evident.

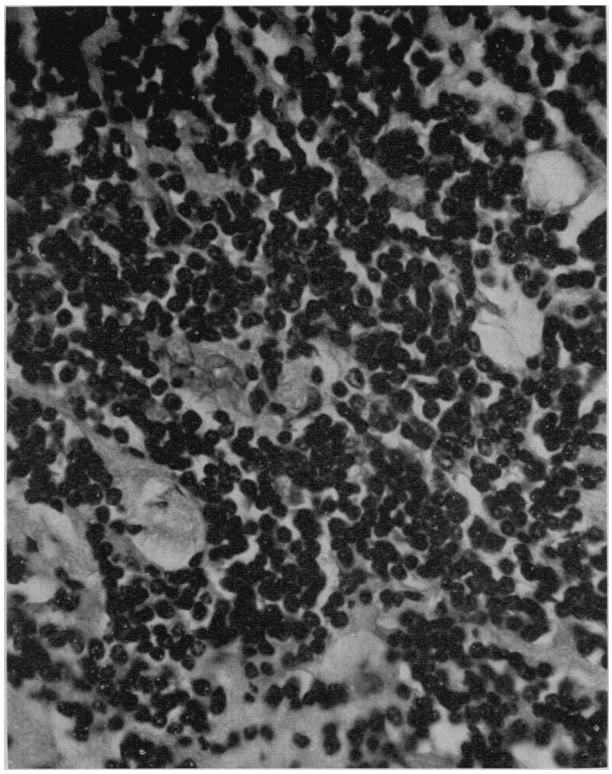

Fig. 12.—Section of moderately enlarged lymph node showing alteration of normal architecture by infiltration of atypical small lymphocytoid-reticulin cells.

aerogenes, Clostridium welchii and *E. coli* from liver, blood, and peritoneal cavity. The bowel was distended, deep bluish and congested throughout, but was not obstructed.

Thrombosis and rupture of the superior pancreaticoduodenal artery was the source of the 500 c.c. of blood found in the lesser sac. There were two litres of bloody fluid in the abdominal cavity. Fig. 9 shows the antemortem thrombosis which had occluded the lumen of the superior pancreatico-duodenal artery. The rupture of the wall at the site of hemorrhage into the abdominal cavity is seen at the lower right of the photograph.

The liver weighed 2200 g., and from the cut surface bubbles of gas exuded. Fig. 10 shows the antemortem septic necrosis of the liver with many visible bacteria in the areas of the cellular change. Fig. 11 shows a liver portal infiltrate with small atypical "naked" lymphocytes of the "lymphocytoid-reticulin" type seen in macroglobulinemia. A small portal venous radicle is seen distended by gas.

Fig. 12 is a section of one of the many moderately enlarged lymph nodes found throughout the body. The normal architecture is changed by an infiltration of atypical small lymphocytoid-reticulin cells.

The spleen was moderately firm and congested in appearance. Figs. 13 and 14 show low- and high-power views of focal splenic subcapsular septic necrosis, with stained bacteria in the areas of cellular change.

The marrow aspiration biopsies taken during the hospital admissions were considered to be non-diagnostic. Fig. 15 is a low-power view of a marrow section at necropsy showing proliferation of abnormal lymphocytoid-reticulin cells with some invasion of the periosteum.

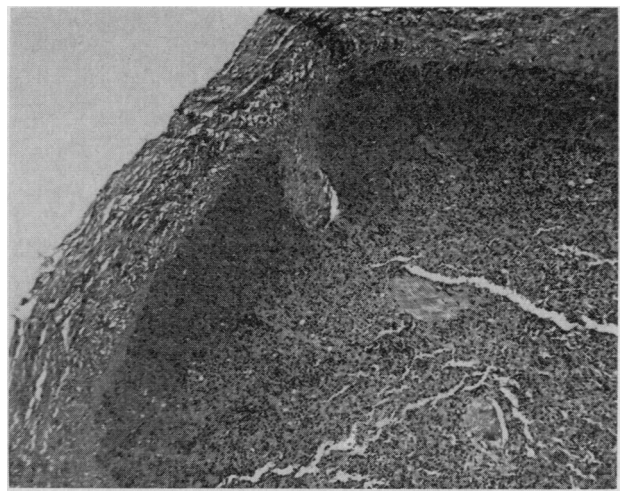

Fig. 13.—Low-power view of focal splenic subcapsular septic necrosis with stained bacteria in areas of cellular change.

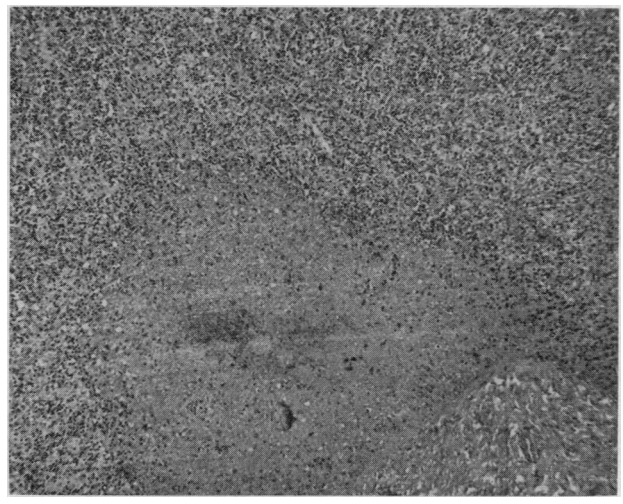

Fig. 14.—High-power view of focal splenic subcapsular septic necrosis depicted in Fig. 13.

DISCUSSION

This rare neoplastic disorder of the reticuloendothelial system is usually characterized by anemia, dyspnea, mucous membrane bleeding, recurrent infection, lassitude and weight loss. It is related to myeloma and lymphoma but is accompanied by moderate lymphadenopathy of smaller size than that seen in lymphoma, and in contrast to myeloma there is only mild osteoporosis without bone pain. Pallor, hepatosplenomegaly and retinal hemorrhage may be found in about 70% of cases,[2] and purpura may be found in over 50%.[2] Edema is also common, being found in 50% of cases.[2] Bleeding from the nose and gums is present in nearly 90%, and not uncommonly the patient may awaken in the morning with a mouthful of blood and moderate nosebleed.[3]

Stupor, designated as "coma paraproteinemica", is noteworthy in the terminal stages of 60% of cases reported in the literature.[2]

The usual laboratory findings include normocytic anemia in which a shortened peripheral

Fig. 15.—Low-power view of a marrow section at necropsy showing proliferation of abnormal lymphocytoid-reticulin cells with some invasion of periosteum.

erythrocyte survival can be demonstrated, and this is often associated with leukopenia and thrombocytopenia. The commonly found bleeding tendency in these patients is considered to be of obscure etiology[1, 2] if it is not attributed to thrombocytopenia, and the capillary fragility test is positive. A striking feature in many patients, including our own, is a marked increase in serum viscosity[1, 2] leading to the appearance of "sausage segmentation" of arterioles on retinoscopic examination.

The erythrocyte sedimentation rate (ESR) is markedly increased except in the 45% of cases in which macroglobulins may also be cryoglobulins. If the cryoglobulins, which may be present in concentrations from a trace to 10 g. %, are present in large quantity, the ESR may be low.[1, 2]

Other fairly common laboratory abnormalities include false-positive serological tests for syphilis, positive agglutination tests, and hyperuricemia.

There may be a decrease in the residual serum gamma globulin, and Bence Jones proteinuria is present in about one-third of cases.[2]

The simplest clinical test to detect abnormal amounts of macroglobulins is the Sia test, which is positive when a precipitate forms after adding one drop of serum to 10-100 c.c. of cold distilled water. Only about 75% of cases have a positive Sia test.

Paper electrophoresis shows a discrete homogeneous peak in either the gamma or beta zone, but this is indistinguishable from that in serum from patients with multiple myeloma. The most specific diagnostic measures are ultracentrifugation studies and immunoelectrophoresis with anti-macroglobulin serum. Macroglobulins are not a homogeneous group of proteins and vary in their amino acid content and immunochemical reaction. They reacted with 19 S (also called β_2M) macroglobulin serum in 66 of 68 cases from several series[2] and in occasional cases have reacted to 7 S unit gamma globulin serum.

Attempts at treatment with steroids, plasmaphoresis, penicillamine depolymerization and alkylating agents have met with success over variable transient periods. Chlorambucil has been of value according to two reports.[5, 6]

The finding of portal venous gas in the antemortem abdominal radiographs was of considerable interest, since only 14 cases with this finding, up to the time of this report, have been reported in adult life, seven in the North American literature[8-10] and seven in the British literature.[11-13] Seven cases have also been reported in infancy,[7, 8] associated with such conditions as intestinal obstruction, gastroenteritis and erythroblastosis.

In adults, as pointed out by Wiot and Felsun,[9] distension, congestion and necrosis of the small intestine frequently accompany gas in the portal system. The latter finding usually signifies mesenteric vascular occlusion, often with accompanying Gram-negative bacteremia with gas formation. It is a sign of ominous import and suggests that death may ensue within 24 hours, though one patient survived for seven days.[9] Guyer and Grainger[12] considered that the radiological sign of gas in the portal venous system should be regarded as indicating severe intestinal-wall damage or necrosis; one common cause of this type of lesion is superior mesenteric vascular occlusion, and the other is necrotizing enteritis.

Closed-loop obstruction and volvulus might also produce this sign if the venous drainage was not completely interrupted, but such an association has not yet been recorded. Diabetic coma[9] and acute hemorrhagic pancreatitis[10] have been reported in association with the sign of portal venous gas.

It is considered that "pneumatosis cystoides intestinalis" with intramural intestinal gas is a separate condition of different etiology though it has been occasionally reported in association with the finding of portal venous gas.[9]

Gas in the biliary radicles as a sign of cholecystoenteric fistula, or rarely ascending cholangitis, may be mistaken for portal venous gas. The differences in radiologic appearance in these two conditions have been clearly delineated as follows:[8-11]

(a) Portal venous gas appears as linear reticular radiolucencies in the right upper quadrant extending to the periphery of the liver shadow; this was probably due to centrifugal blood flow.[8]

(b) Biliary tree gas is located in large channels and appears caudally and centrally, often with gas present in the common bile duct and gallbladder if these structures are present. It is thought to be limited by centripetal bile flow.[8]

The explanation for the presence of gas in portal veins is still controversial. Wiot and Felsun[9] favoured the theory that gas-forming bacteria gain entry to mesenteric veins across damaged vascular walls and then generate gas, *in situ*, in the liver.

Other workers[7, 8] consider that the gas "embolizes" into the mesenteric veins from intestinal intraluminal gas, in the presence of necrotic bowel with gaseous distension and bacterial infection of the gut by gas-forming organisms of the coliform group.

Our patient could be considered to have had a tendency towards vascular occlusion as evidenced by the marked increase in serum viscosity possibly associated with the mesenteric arterial occlusion. Of equal importance was this patient's tendency towards recurrent pulmonary bacterial infections, with the later appearance of Gram-negative septicemia as shown by the postmortem findings of widespread focal septic necrosis. Rapid and increasing development of portal venous gas was demonstrated in two abdominal flat plates taken less than one hour apart.

This clinical sign could logically be expected to occur in patients suffering from disorders similar to that of the patient described in the foregoing report, which, it is hoped, may stimulate increased awareness of this sign.

SUMMARY

The clinical course and biochemical findings in a case of primary macroglobulinemia are presented. The autopsy and radiologic features of gas in the portal venous system associated with mesenteric vascular occlusion, bowel distension and congestion, and Gram-negative bacteremia are reviewed in detail.

The authors wish to express their thanks to Dr. T. Kasper for his help in the pathologic assessment of this case, and to Dr. D. J. Campbell, Dr. C. Kay and Mrs. E. Neumann in regard to the biochemical investigations. Dr. C. B. Godberson, the referring physician, is also thanked for his co-operation and help in following this case, as is the Edmonton division of the Alberta Cancer Diagnostic Clinic.

REFERENCES

1. ROSEN, F. S.: *New Eng. J. Med.*, **267**: 491, 1962.
2. SCHUR, P. H. AND APPEL, L.: *New York J. Med.*, **61**: 2431, 1961.
3. RITZMANN, S. E. *et al.*: *A.M.A. Arch. Intern. Med.*, **105**: 939, 1960.
4. MARTIN, N. H.: *Quart. J. Med.*, **29**: 179, 1960.
5. BAYRD, E. D.: *Proc. Mayo Clin.*, **36**: 135, 1961.
6. CLATANOFF, D. V. AND MEYER, O. O.: *J. A. M. A.*, **183**: 40, 1963.
7. WOLFE, J. N. AND EVANS, W. A.: *Amer. J. Roentgen.*, **74**: 486, 1955.
8. SUSMAN, N. AND SENTURIA, H. R.: *Ibid.*, **83**: 847, 1960.
9. WIOT, J. F. AND FELSON, B.: *Ibid.*, **86**: 920, 1961.
10. SISK, P. B.: *Radiology*, **77**: 103, 1961.
11. BARRETT, A. F.: *Clin. Radiol.*, **13**: 92, 1962.
12. GUYER, P. B. AND GRAINGER, K.: *Brit. J. Radiol.*, **36**: 379, 1963.
13. STEWART, J. O. R.: *Brit. Med. J.*, **1**: 1328, 1963.