3. THUDIUM VF, PEARSON RE: *Drug Information Services: Two Operational Models.* Model II. A regional drug information service network. US Dept of Health, Education and Welfare, publ no (HSM) 72-3030, 1972, p 195
4. KING CM, HELLUMS BA: *Drug Information Services: Two Operation Models.* Model I. A complete drug information service in a hospital. US Dept of Health, Education and Welfare, publ no (HSM) 72-3030, 1972, p 1
5. KLAPPER MS, PAKARD JM, SHEEKY TW: MIST: a two-year report. *J Med Assoc State Ala* 41: 447, 1971
6. *Extra Pharmacopoeia: Martindale,* TODD RG, BLACOW NW (eds), London, Pharm Pr, 1967
7. TESTER WM, OLESON CH: Microfilm file forms data base. *Hospitals* 45: 18, 1971
8. BRODIE DC: *Drug Utilization and Drug Utilization Review and Control,* National Center for Health Services, research bull RO-70-8, Rockville, MD, 1970, p 3
9. OGILVIE RI, REUDY J: Adverse drug reactions during hospitalization. *Can Med Assoc J* 97: 450, 1967
10. MILLER RR: Hospital admissions due to adverse drug reactions. *Arch Intern Med* 134: 219, 1974
11. ROSENBERG JM, GUZZETTE PJ, ZUPKO AG: Pharmacist-manned drug information centres are increasing. *Pharm Times* 40: 43, 1974
12. LALONDE M: *A New Perspective on the Health of Canadians,* Ottawa, Government of Canada, 1974, p 71

Addendum

As of Apr. 30, 1976 the dial-access drug information service had received 546 requests for drug information, an average of 30 calls per month. The sources of the calls were as follows: physicians, 32%; community pharmacists, 47%; hospital pharmacists, 15%; and others, 6%.

Miliary tuberculosis presenting with hyponatremia and thrombocytopenia

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A 74-year-old woman with miliary tuberculosis had moderately severe hyponatremia due to inappropriate secretion of antidiuretic hormone (SIADH) and very severe thrombocytopenia without other hematologic abnormalities. She was treated with isoniazid, rifampin, ethambutol, prednisone, vincristine and fluid restriction and recovered completely.

The SIADH may have been a response by the posterior pituitary to a decrease in intravascular volume resulting from the extensive pulmonary disease or associated hypoxia, or the tuberculous lung may have released ADH or an ADH-like substance. The thrombocytopenia may have resulted from a direct or indirect toxic effect of infection or, less likely, the tuberculosis may have activated latent idiopathic thrombocytopenic purpura.

Une femme de 74 ans, atteinte de tuberculose miliaire, a présenté une hyponatrémie modérément grave attribuable à une sécrétion inadéquate d'hormone antidiurétique et une thrombocytopénie très sévère en l'absence de toute autre anomalie hématologique. Elle s'est rétablie complètement à la suite d'un traitement associant isoniazide, rifampine, éthambutol, prednisone, vincristine et restriction hydrique.

Le syndrome de sécrétion inadéquate d'hormone antidiurétique peut avoir été une réponse de la pituitaire postérieure à une diminution du volume intravasculaire consécutive à l'étendue de l'atteinte pulmonaire ou à l'hypoxie qui en a résulté, ou encore, le poumon tuberculeux peut avoir libéré de l'hormone antidiurétique ou une substance analogue. La thrombocytopénie peut avoir résulté d'un effet toxique direct ou indirect de l'infection ou, moins probablement, la tuberculose peut avoir activé un purpura thrombocytopénique idiopathique latent.

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Both hyponatremia and thrombocytopenia are know to be associated with tuberculosis. Non-Addisonian hyponatremia and hypochloremia were well described almost 40 years ago.[1] In 1965 the mechanism of the hyponatremia in the majority of such cases was demonstrated to be inappropriate secretion of antidiuretic hormone (ADH).[2] In one group of 522 new patients with pulmonary tuberculosis hyponatremia was detected in 10.7%; it was more common in blacks than in whites and in males than in females.[3] The serum sodium concentration was usually only slightly decreased (125 to 135 mmol/*l*) and only two patients (0.4%) had a value of less than 125 mmol/*l*. The syndrome of inappropriate secretion of ADH (SIADH) is probably more common in patients with tuberculous meningitis.[4,5]

Thrombocytopenia, on the other hand, is very uncommon in patients with tuberculosis. In 1952 a review of the literature revealed 31 instances of this association:[6] 11 of the patients had pulmonary tuberculosis; 10, tuberculous splenitis; and 10, miscellaneous types of tuberculosis. At the time of a case report of thrombocytopenic purpura in a patient with tuberculous lymphadenitis in 1964[7] approximately 40 cases of thrombocytopenia in association with tuberculosis had been reported. Since then there have been no similar cases reported other than those associated with pancytopenia,[8-10] disseminated intravascular coagulation,[11] underlying hematologic disease[12-14] or antituberculous therapy.[15]

We recently treated an elderly woman with miliary tuberculosis who presented with moderately severe hyponatremia and very severe thrombocytopenia without anemia, leukopenia, hematologic disease or splenomegaly.

Case report

A 74-year-old Chinese woman was admitted to St. Paul's Hospital July 11, 1974 with a diagnosis of acute atrial fibrillation.

She had been well all her life except for mild recurrent episodes of right upper quadrant abdominal pain and indigestion for the past 5 years. She had had no previous hospitalizations and had no history of a bleeding tendency. In the past year no medications had been used except a barbiturate. A chest radiograph in May 1974 had been normal. Her father and one brother had died of tuberculosis and one daughter had been treated for tuberculosis.

The present illness consisted of a 2-week history of malaise, fatigue, anorexia and weakness. Because of basal rales and a chest radiograph suggestive of pulmonary congestion, digoxin, 0.25 mg daily, had been administered for 1 week prior to admission.

She was diaphoretic and tachypneic and had atrial fibrillation. Digoxin, 0.5 mg,

was given intravenously and two doses of furosemide (40 mg) were administered orally in the first 24 hours. Periods of regular supraventricular tachycardia without block developed and digitalis intoxication was suspected. All medications were discontinued and the cardiac rhythm soon returned to normal.

During the next 6 days she received only a barbiturate sedative for sleep. Malaise, anorexia and lethargy continued, and moderate right upper quadrant abdominal pain recurred. Intermittent tachypnea on minimal exertion was noted. A fever developed on the 3rd hospital day. The respiratory service was consulted on the 8th hospital day, when the chest radiograph was interpreted as suggesting miliary tuberculosis. The patient denied any respiratory symptoms.

She was not in acute distress. Pulse rate was 100 beats/min and the rhythm, regular; blood pressure was 140/90 mm Hg; respirations were 24/min; and the temperature was 39°C. Bilateral pulmonary basal crepitations, more pronounced on the right, were noted. The cardiovascular system was normal. The abdomen was moderately tender in the right upper quadrant, with mild guarding and no rebound tenderness. Liver and spleen were not palpable and the bowel sounds were normal. Although she was slightly confused, results of neurologic examination were otherwise normal. Bruising and oozing were noted at venipuncture sites. A few petechiae were seen on the extremities and many on the buttocks and in the sacral region. There was no edema.

The hemoglobin value was 11.8 g/dl with normal erythrocyte indices and unremarkable morphology. The leukocyte count was 8.6 x $10^9/l$; polymorphonuclear forms predominated. Platelet count was less than 1 x $10^9/l$. Prothrombin time was 13 s (control time, 12.5 s) and the partial thromboplastin time, 46 s (control time, 36 s). The following values for serum constituents were determined: sodium, 119 mmol/*l*; potassium, 3.9 mmol/*l*; chloride, 80 mmol/*l*; total CO_2 content, 28 mmol/*l*; bilirubin, 1.7 mg/dl (normal, less than 1 mg/dl); and alkaline phosphatase, 146 IU/*l* (normal, 30 to 100 IU/*l*). Blood urea nitrogen value was 18 mg/dl. Serum osmolality was 247 mOsm/*l*.

The specific gravity of the urine was 1.026. There were four to eight leukocytes per high-power field and a trace of protein in the urine. The following values of urine constituents were determined: sodium, 2.4 mmol/*l*; potassium, 38 mmol/*l*; and chloride, 1.5 mmol/*l*. The urine osmolality was 696 mOsm/*l*.

Electrocardiogram showed normal sinus rhythm and ischemic changes. Chest radiograph showed slight cardiomegaly and a miliary pattern in the lungs. The abdominal film and cholangiogram demonstrated the gallbladder to be calcified and nonfunctioning. Bone marrow aspirate showed slight hypercellularity, especially of the myeloid series, and abundant megakaryocytes in all stages of maturity. No granulomata or acid-fast bacilli were seen. A tuberculin skin test (with 5 tuberculin units of purified protein derivative of tuberculin) was negative at 48 hours.

The presumptive diagnosis was miliary tuberculosis with secondary thrombocytopenia and SIADH. Daily doses of prednisone, 100 mg, isoniazid, 300 mg, rifampin, 600 mg, ethambutol, 1200 mg, and pyridoxine, 25 mg, were commenced. Six units of platelets were infused intravenously overnight and fluids were restricted to a total of 700 ml daily. The next day the temperature returned to normal and the platelet count remained low, at 3 x $10^9/l$.

On the 12th hospital day previous gastric washing specimens were reported positive on smear for acid-fast bacilli. Eventually two of three gastric washings were positive on culture for *Mycobacterium tuberculosis*, but four urine cultures and a bone marrow culture were negative. Sputum was not obtainable.

On the 14th hospital day gross blood was noted in the stool and the hemoglobin value decreased to 8.5 g/dl. Five units of packed blood cells were required during the next 3 days to maintain the hemoglobin value at more than 10 g/dl.

By the 19th day the serum sodium value was 130 mmol/*l* and the platelet count, 2 x $10^9/l$. Vincristine, 1 mg, was then infused intravenously. The platelet count increased to 72 x $10^9/l$ over the next 6 days and the patient's clinical status slowly began to improve.

Over the next 7 weeks the prednisone dose was tapered, then the drug was discontinued. The platelet count remained greater than 180 x $10^9/l$ and the serum sodium value, greater than 137 mmol/*l* (Fig. 1). Serum bilirubin and alkaline phosphatase values returned to normal (0.6 mg/dl and 80 IU/*l*, respectively). The chest radiograph improved greatly over this period (Figs. 2 and 3). The patient was discharged feeling well and receiving triple-drug antituberculous therapy, after 79 days in hospital.

Discussion

Hyponatremia appears to be fairly commonly associated with tuberculosis. Although a few cases may be due to tuberculous adrenalitis and other less common causes of a low serum sodium concentration, the majority are attributable to SIADH.[2,3,16] Hyponatremia, hypo-osmolar serum, hyperosmolar urine, absence of renal or adrenal disease, and correction with fluid restriction fulfil the criteria for the diagnosis of this syndrome in our patient.[17] A lack of significant sodium wasting in the urine may occur with SIADH and is thought to be due to the reaching of a new steady state of equilibrium at a low serum sodium concentration.[17]

ADH is normally released from the posterior pituitary in response to increased serum osmolality or decreased intravascular volume. The latter is thought to be the more important. There are several possible reasons for the inappropriate release of ADH in patients with tuberculosis. It is most likely that, in patients with tuberculous meningitis, ADH is released directly from the posterior pituitary, as in many diseases affecting the central nervous system.[17] SIADH in pulmonary tuberculosis and in other infectious pulmo-

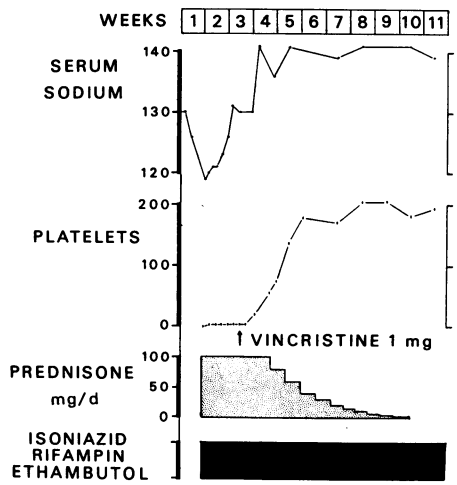

FIG. 1—Serum sodium values (mmol/*l*), platelet counts (x $10^9/l$) and chemotherapy during hospital stay of patient with miliary tuberculosis, hyponatremia and thrombocytopenia.

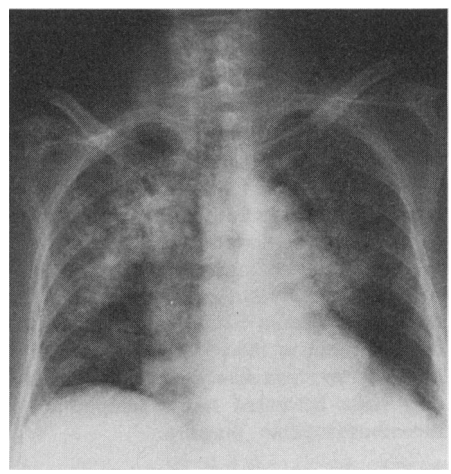

FIG. 2—Diffuse miliary pattern in lungs before therapy.

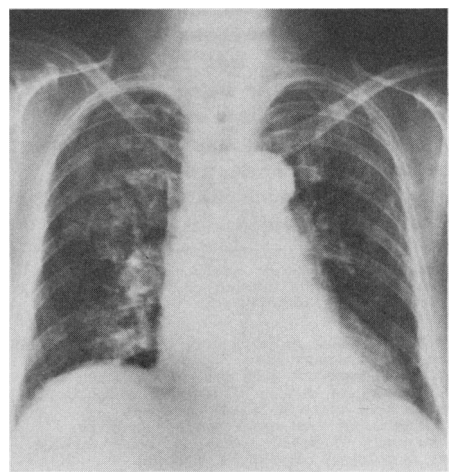

FIG. 3—Great improvement by time of discharge.

nary diseases may result from changes in blood pressure and flow in intrathoracic vessels and the left atrium, in which the receptors that sense changes in intravascular volume are probably located.[18] This may relate directly to the extent of pulmonary disease or to associated hypoxia, which leads to pulmonary vasoconstriction and, hence, changes in blood flow.[18] Another possibility is direct release from the tuberculous lung of ADH or an ADH-like substance similar to that released from some small-cell bronchogenic carcinomas.[19] Such a substance has been demonstrated in the lung and urine of a patient with pulmonary tuberculosis.[16] These mechanisms do not explain the recently described appearance of this syndrome in a patient with tuberculosis localized to bone.[20]

Diuretic response to water loading was found to be impaired in five of six patients with pulmonary tuberculosis and a history of ethanol abuse.[21] It is possible that ethanol contributes both to an acquired defect in ADH release and to an increased susceptibility to tuberculosis. Withdrawal from ethanol can apparently result in a rebound oversecretion of ADH following the ethanol-induced suppression of ADH release.[22] "Stress" has been thought to cause release of ADH in patients treated by positive-pressure ventilation[23] and could possibly have this effect in other critically ill patients.

Therapy for SIADH is restriction of total fluids in the mild to moderate case.[17] Most severe and symptomatic cases should be treated with careful infusion of hypertonic saline, or with the concomitant use of hypertonic saline and a potent diuretic such as furosemide.[24] In our patient stringent fluid restriction alone resulted in return of the serum sodium concentration to an acceptable value (130 mmol/*l*) in 1 week.

Thrombocytopenia may accompany tuberculosis as a result of a number of factors. First, bone marrow involvement with tuberculosis may be extensive enough to result in pancytopenia.[6] Second, tuberculous splenitis may occur and is often associated with splenomegaly and pancytopenia.[6] Third, an underlying hematologic disease, such as leukemia, may cause thrombocytopenia and may predispose to tuberculous infection.[12-14] Fourth, disseminated intravascular coagulation occurs rarely in miliary tuberculosis.[11] Fifth, a reaction to antituberculous drugs, most notably rifampin,[15] may lead to thrombocytopenia. Sixth, tuberculosis may cause or activate latent idiopathic thrombocytopenic purpura (ITP).[7] Seventh, a direct or indirect toxic effect of infection has recently been suggested as the cause of thrombocytopenia in a case of mumps[25] and could occur in other toxic infections.

In our patient the absence of pancytopenia, nonpalpability of the spleen and the absence of tubercle bacilli in the bone marrow aspirate tend to rule out the first two causes. However, it is possible for tuberculosis in the spleen to be associated with thrombocytopenia without anemia, leukopenia or splenomegaly.[6,26] Whether, in this situation, the splenic tuberculosis and the thrombocytopenia are directly related cannot easily be answered. Our patient most likely had some tuberculous involvement of liver and spleen but had no evidence of hypersplenism. There is no support for the third, fourth or fifth possibility in this patient.

We are therefore left with the hypothesis that this patient's thrombocytopenia was probably due to one of the last two causes, ITP or toxic thrombocytopenia of infection. ITP is thought to be due to a cytotoxic antibody, usually IgG, directed against platelets.[27] It generally occurs following infection, most often viral, and is more common in childhood.[28] Toxic thrombocytopenia is thought to be due to a direct effect of the infecting organism or of immune complexes on the platelets.[26] This type tends, therefore, to occur at the most toxic period in the infection, rather than after the infection, as in ITP.[28]

The treatment of thrombocytopenia consists of supportive care, with platelet and blood transfusions, and — more important — therapy for the underlying disease. Therapy directed towards increasing the platelet count includes adrenocortical steroids, which are particularly valuable when an immune or an inflammatory mechanism is the cause. In addition, steroids may treat the underlying disease. Before steroids result in an increase of the platelet count they are believed to exert a protective stabilizing effect on the vascular endothelium.[29] Splenectomy may be effective in reversing thrombocytopenia due to enhanced destruction in up to 90% of cases.[29] Recently vincristine has been shown to be very useful in the therapy of idiopathic and several forms of secondary thrombocytopenia resistant to steroids and splenectomy.[30] Our patient was treated with three antituberculous drugs, platelets, blood and prednisone. When the platelet count failed to increase after 10 days of this therapy, 1 mg of vincristine was given. Since the patient continued to receive the other four medications, it is difficult to assess the importance of the vincristine in the increase of the platelet count in the week following its administration. However, the timing of the response is similar to that seen in patients responding to vincristine[30] and it is therefore possible that this drug may have some efficacy in one further form of secondary thrombocytopenia.

References

1. WINKLER AW, CRANKSHAW OF: Chloride depletion in conditions other than Addison's disease. *J Clin Invest* 17: 1, 1938
2. WEISS H, KATZ S: Hyponatremia resulting from apparently inappropriate secretion of antidiuretic hormone in patients with pulmonary tuberculosis. *Am Rev Respir Dis* 92: 609, 1965
3. CHUNG DK, HUBBARD WW: Hyponatremia in untreated active pulmonary tuberculosis. *Am Rev Respir Dis* 99: 595, 1969
4. RAPOPORT S, WEST CD, BRODSKY WA: Salt losing conditions: the renal defect in tuberculous meningitis. *J Lab Clin Med* 37: 550, 1951
5. CHEEK DB: Total body chloride in tuberculous meningitis. *Pediatrics* 14: 87, 1954
6. ELLMAN P, JOHNSON JHP: Tuberculosis and purpura. *Br J Tuberc* 46: 214, 1952
7. LEVY M, COOPER BA: Thrombocytopenic purpura associated with tuberculous lymphadenitis. *Can Med Assoc J* 90: 373, 1964
8. FISHER AM, OSSMAN AG, WILGIS EFS, et al: Generalized tuberculosis with pancytopenia. *Bull Johns Hopkins Hosp* 119: 355, 1969
9. MIGUERES J, BOUISSOU H, JOVER A, et al: Pancytopénie et tuberculose aiguë nécrotique. *Rev Tuberc (Paris)* 33: 265, 1969
10. MANGION PG: Disseminated tuberculosis complicated by pancytopenia. *Proc R Soc Med* 64: 1000, 1971
11. MAVLIGIT GM, BINDER RA, CROSBY WH: Disseminated intravascular coagulation in miliary tuberculosis. *Arch Intern Med* 130: 388, 1972
12. GLASSER RM, WALKER RI, HERION JC: The significance of hematological abnormalities in patients with tuberculosis. *Arch Intern Med* 125: 691, 1970
13. HANSSON V, SVANE S, TORGENSEN O: Nonreactive tuberculosis and malignant blood disorders. *J Oslo City Hosp* 22: 5, 1972
14. COBURN RJ, ENGLAND JM, SAMSON DM, et al: Tuberculosis and blood disorders. *Br J Haematol* 25: 793, 1973
15. POOLE G, STRADLING P, WORLLEDGE S: Potentially serious side effects of high-dose twice weekly rifampin. *Br Med J* 1: 765, 1972
16. VORHERR H, MASSRY SG, FALLET R, et al: Antidiuretic principle in tuberculous lung tissue of a patient with pulmonary tuberculosis and hyponatremia. *Ann Intern Med* 72: 383, 1970
17. BARTTER FC, SCHWARTZ WB: The syndrome of inappropriate secretion of antidiuretic hormone. *Am J Med* 42: 790, 1967
18. ROSENOW EC, SEGAR WE, ZEHR JE: Inappropriate antidiuretic hormone secretion in pneumonia. *Mayo Clin Proc* 47: 169, 1972
19. VORHERR H, MASSRY SG, UTIGER RD, et al: Antidiuretic principle in malignant tumor extracts from patients with inappropriate ADH syndrome. *J Clin Endocrinol Metab* 28: 162, 1968
20. HEATON DC: Inappropriate secretion of antidiuretic hormone in infectious pulmonary disease. *Med J Aust* 2: 110, 1972
21. SHALHOUB RJ, ANTONIOU LD: The mechanism of hyponatremia in pulmonary tuberculosis. *Ann Intern Med* 70: 943, 1969
22. SERENY G, RAPOPORT A, HUSDAN H: The effect of alcohol withdrawal on electrolyte and acid-base balance. *Metabolism* 15: 896, 1966
23. KHAMBATTA HJ, BARATZ RA: IPPB, plasma ADH and urine flow in conscious man. *J Appl Physiol* 33: 362, 1972
24. HANTMAN D, ROSSIER B, ZOHLMAN R, et al: Rapid correction of hyponatremia in the syndrome of inappropriate secretion of antidiuretic hormone. *Ann Intern Med* 78: 870, 1973
25. GRAHAM DY, BROWN CH, BENRY J, et al: Thrombocytopenia. A complication of mumps. *JAMA* 227: 1162, 1974
26. KALINOWSKI SZ, WALKER JM: Thrombocytopenic purpura in tuberculosis. *Br J Tuberc* 50: 239, 1956
27. KARPATKIN S, SISKIND GW: *In vitro* detection of platelet antibody in patients with idiopathic thrombocytopenic purpura and systemic lupus erythematosis. *Blood* 33: 295, 1969
28. CHOI SI, MCCLURE PD: Idiopathic thrombocytopenic purpura in childhood. *Can Med Assoc J* 97: 562, 1967
29. ASTER JH: Thrombocytopenia due to enhanced platelet destruction (chap 139), in *Haematology*, WILLIAMS WJ, BEUTLER E, ERSLEV AJ, et al (eds), New York, McGraw, 1972
30. AHN YS, HARRINGTON WJ, SEELMAN RC, et al: Vincristine therapy of idiopathic and secondary thrombocytopenias. *N Engl J Med* 291: 376, 1974