Primary Malignant Reticulosis of the Brain in Wiskott-Aldrich Syndrome

Report of a Case

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In 1937 Wiskott originally described the combination of eczema, thrombocytopenia, and increased susceptibility to infection in 3 brothers. Aldrich, Steinberg, and Campbell (1954) subsequently characterized this syndrome as a sex-linked recessive disorder, describing a family which included 40 males, 16 of whom died in infancy, and 10 of whom were known to have had eczema, otitis, and bloody diarrhoea.

Pathological features of this syndrome include haemorrhage involving the gastro-intestinal tract, skin, adrenal glands, or brain; purulent otitis, pneumonitis, and meningitis; lymphadenopathy, splenomegaly, and thymic atrophy, or fibrosis. Histologically, there is a characteristic depletion of lymphocytes in the follicles of the lymph nodes and the Malpighian corpuscles of the spleen, often accompanied by prominent reticuloendothelial hyperplasia, and infiltration of the visceral organs and brain by reticulum cells, plasma cells, and histiocytes (Coleman, Leikin, and Guin, 1961; Huntley and Dees, 1957; Kildeberg, 1961; Krivit and Good, 1959; ten Bensel, Stadlan, and Krivit, 1966; Wolff, 1967).

The development of malignant systemic reticulo-endotheliosis and lymphoma in children with Wiskott-Aldrich syndrome has been described (Chaptal *et al.*, 1966; Diamond, 1966; Kildeberg, 1963; Pearson *et al.*, 1965; ten Bensel *et al.*, 1966). It is the purpose of this report to record an example of this syndrome with malignant reticulosis limited to the central nervous system.

Case History

This male infant was born at term after an uneventful pregnancy, weighing 3.2 kg. Delivery was complicated

by polyhydramnios and a shoulder presentation, necessitating internal version under general anaesthesia. He breathed spontaneously. Petechiae ascribed to birth trauma were noted over the head and neck but quickly cleared.

He was breast-fed and did well until 3 weeks of age, when oatmeal, rice cereal, and evaporated milk were added to his diet. He rapidly developed blood-tinged diarrhoea and a pin-point papular and pustular facial rash, particularly severe about the ears. Milk was discontinued, and the diarrhoea improved. Throughout the remainder of his life, intolerance to most foods continued and he lived primarily on rice, rice products, baked potatoes, and soy formula.

At 5 weeks of age he developed external otitis and a petechial rash. Laboratory tests showed Hb 9.2 g./100 ml., WBC 21,000/cu.mm. (10% eosinophils), and platelets 8000/cu.mm. The bone-marrow was regarded as normal, though a diagnosis of megakaryocytic hyperplasia was entertained. By 3 months of age he had petechiae over his entire body, an eczematous rash over the neck, ears, and antecubital fossae, and a firm spleen, palpable 4 cm. below the costal border, but no lymphadenopathy or hepatomegaly. The bone-marrow was normal, including the number and morphology of megakaryocytes. Skin biopsy showed no histiocytosis. Neither serum precipitins to milk or wheat proteins nor isohaemagglutinins were found. A chest x-ray was normal and showed a normal thymic shadow.

Over the next 2½ years he did poorly, with frequent infections, especially otitis, a constant petechial rash (platelet counts between 10,000 and 50,000/cu.mm.), and eczema of varying severity. Even with a markedly limited diet, a kaolin-pectin preparation was often required to control diarrhoea. At 15 months he was exposed to a sensitizing dose of dinitrofluorobenzene but failed to react to subsequent challenge. He developed antibodies following *Salm. typhosa* immunization.

At 2½ years of age he was in hospital with bilateral otitis media and pneumonia. Meningitis was diagnosed on the second hospital day. The CSF contained 3000 WBC (98% polymorphonuclear leucocytes) and 100 RBC/cu.mm., less than 5 mg./100 ml. glucose, and

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114 mg./100 ml. protein. *Pseudomonas* was cultured from the CSF, blood, and skin. He was treated with polymyxin intrathecally (5 mg. initially, 2.5 mg. every other day), and intravenously (16 mg. every 12 hours) for 45 days. CSF glucose returned to normal in one week; protein levels fell to normal in one week, but rose again and remained at approximately 100 mg./100 ml.; pleocytosis disappeared, and cultures were sterile after 40 days of therapy.

Thereafter, weekly CSF examinations showed 0-4 WBC/cu.mm., normal glucose levels, 80-318 mg./100 ml. protein, and sterile cultures. He continued to have daily temperature spikes, progressive splenomegaly, but no hepatomegaly. The bone-marrow showed erythroid hyperplasia but was otherwise normal. Chest x-rays showed an unchanging infiltrate in the left lower lobe and lingula. On the 87th hospital day he developed severe epistaxis, for which 250 ml. whole blood was given. Thereafter he improved, splenomegaly decreased, and he was discharged on the 99th hospital day.

He was readmitted 11 days later with fever, malaise, and oral bleeding. On the next day his pupils became unequal and he began to 'pick at the air'. Haematocrit, Hb, WBC, serum electrolytes, and blood urea nitrogen were normal. CSF was clear yellow, with 4 WBC/cu.mm., 145 mg./100 ml. protein, and 40 mg./100 ml. glucose. Bacterial and fungal cultures were sterile. Blood, urine, nasal, pharyngeal, and stool cultures failed to grow pathogens. His level of consciousness fluctuated over the next 2 days and he died early on the third day in hospital, at the age of 3 years and 1 month.

Pathological Observations

The body was thin and wasted, weighing 10.5 kg. Cervical, axillary, and inguinal lymph nodes were enlarged to 2.0 cm. in diameter. The thymus gland was not found. The lungs were firm, heavy, and non-crepitant; their cut surfaces were wet and mottled, and numerous small scattered abscesses were seen. The liver weighed 600 g. In the left lobe there were two yellow-grey circumscribed areas, 1.0 cm. and 1.5 cm. in diameter. The spleen weighed 170 g. and was firm and elastic; the cut surface had a homogeneous appearance.

Bacterial cultures from the lungs and brain showed a heavy growth of klebsiella, aerobacter, and *Pseudomonas aeruginosa* organisms.

The brain weighed 1000 g. The leptomeninges were congested and were stained deep yellow at the base of the brain, most prominently over the interpeduncular fossa. There was no uncal or cerebellar herniation. An intracerebral haematoma measuring 3.0 × 1.8 × 2.0 cm. protruded from the medial surface of the brain in the right parieto-occipital region, 4.0 cm. anterior to the occipital tip. Over the orbital surface of the right frontal lobe there was a confluent subpial petechial haemorrhage measuring 4.0 × 4.0 cm. Numerous small petechial haemorrhages were also scattered over the lateral surface of the right parietal lobe.

When the brain was coronally sectioned, haemorrhages measuring up to 2.0 cm. in diameter were found in the heads of both caudate nuclei and the body of the right caudate nucleus, in the left inferior frontal, the left superior temporal, and the right medial orbital gyri. Smaller, punctate haemorrhages measuring 1 to 3 mm. in diameter were found in the periventricular white matter near the atria of the lateral ventricles, in the deep white matter of the frontal, parietal, and occipital lobes, and in the cerebellar hemispheres, basis pontis, and dorsal medulla. There were bilateral cortical softenings over the medial surfaces of the frontal poles, extending from the gyri recti to the inferior surface of the rostrum of the corpus callosum.

Histology. The cerebral leptomeninges were infiltrated by small numbers of lymphocytes, monocytes, plasma cells, and by scattered groups of haemosiderin-filled macrophages. Numerous small blood vessels in the frontal and temporal lobes, basal ganglia, corpus callosum, fornix, and brain-stem were cuffed with polygonal or spheroidal cells containing central spheroidal nuclei, with distinct nuclear membranes and discrete chromatin nets (Fig 1a and b). These cuffs were often 2 to 20 cells thick. In several areas, particularly the frontal and temporal lobes, these cells infiltrated the neural parenchyma irregularly. Mitotic figures were numerous, and cells with bizarre large nuclei, sometimes resembling Reed-Sternberg cells were seen (Fig. 2). Sections stained by silver carbonate impregnation did not show microglia. A slight increase in the number of reticulin fibres was found in the adventitia of blood vessels which were cuffed with malignant reticulum cells. These fibres were not present in the infiltrated brain tissue, which was the seat of a pronounced astrocytic proliferation.

PAS-positive nuclear inclusions were not seen. Small foci of necrosis and haemorrhage were present. The larger haemorrhagic lesions observed on gross examination appeared to be partially composed of necrotic tissue and were irregularly surrounded by a cellular infiltrate similar to that previously described.

Extensive cortical necrosis was found in the left gyrus rectus, the medial part of the left frontal pole, and the left cingulate gyrus. Many ferruginated neurones and calcium deposits were found in the necrotic areas, and large numbers of plump astrocytes were present in the superficial layers of the necrotic cortex.

Selective neuronal loss amounting to almost complete depopulation and accompanied by a very slight astrocytic gliosis was found in the Sommer sector of the hippocampus and in the hippocampal gyrus.

In the pons and medulla there were discrete foci of tissue necrosis surrounded by palisades of reactive histiocytes with elongated nuclei. Necrotic blood vessels with homogeneous eosinophilic walls and thrombosed lumina were seen in these foci. In the surrounding tissue, blood vessels were cuffed with lymphocytes, and there was an increase of capillaries and astrocytes.

FIG. 1a.—Prominent perivascular cuffing in the frontal white matter. (Nissl. $\times 40$.)

FIG. 1b.—Perivascular infiltrate of mononuclear neoplastic cells in brain, at high power. (H. and E. $\times 700$.)

FIG. 2.—In the brain the cellular infiltrate is composed of mononuclear cells with occasional elements resembling Reed-Sternberg cells. (H. and E. $\times 375$.)

In the spinal cord, there was severe fibrous thickening of the leptomeninges, which were partially adherent to the dura and infiltrated with chronic inflammatory cells and haemosiderin-containing macrophages. Microglial nodules were scattered in the cord parenchyma, and were particularly numerous in the anterior horns of the lumbar enlargement. In the cervical and thoracic levels there was severe loss of myelinated axons in the gracile fascicles and the lateral corticospinal tract on one side, accompanied by fibrillary gliosis.

In the lungs there were numerous small areas of haemorrhagic necrosis in which necrotic and thrombosed blood vessels were found. These areas were surrounded by a dense inflammatory infiltrate composed largely of mononuclear cells. In addition, there were scattered foci of bronchopneumonia. In these foci the bronchiolar walls and neighbouring interalveolar septa were thickened and infiltrated by many large mononucleated cells and giant cells of the foreign body type. These cells were also present in bronchiolar and alveolar lumina. Intracytoplasmic and intranuclear inclusions were not seen.

In the liver there were areas of haemorrhagic necrosis, which contained necrotic and thrombosed blood vessels and were surrounded by a dense peripheral rim of chronic inflammatory cells.

In the lymph nodes the normal architecture was lost except for the peripheral sinuses. Lymph follicles and germinal centres were absent, and there was a paucity of lymphocytes. The main cell type consisted of large

reticular cells with clear nuclei and abundant eosinophilic cytoplasm. Plasma cells were present in greater numbers than usual and occasionally formed small aggregations. There was much congestion of the small blood vessels.

Lymphocytes were scarce in the spleen, and the Malpighian bodies consisted almost entirely of reticular cells. Germinal centres were absent. In the red pulp, the endothelial cells lining the sinuses were more prominent than normal, and there were few lymphocytes in the Billroth cords.

Discussion

In our patient, infectious lesions were widespread. *Klebsiella*, aerobacter, and *Pseudomonas aeruginosa* were cultured from the lungs and brain at necropsy. Though these organisms were not shown histologically, the necrotizing changes in the blood vessels of the lungs, liver, and brain-stem were probably related to the pseudomonas septicaemia. The histological demonstration of a giant cell pneumonia suggested a viral infection as well. Root and Speicher (1963) have previously described giant cell pneumonia in a child with Wiskott-Aldrich syndrome. They interpreted the giant cells as Warthin-Finkeldy cells without the concurrence of the typical exanthem of measles.

Lymphocytic depletion and the proliferation of

reticulum cells in lymph nodes and spleen, as seen in this case, have been repeatedly reported in Wiskott-Aldrich syndrome (Coleman *et al.*, 1961; Krivit and Good, 1959; Root and Speicher, 1963; Wolff, 1967). This proliferation of reticulum cells has usually been interpreted as a reactive hyperplasia despite the marked alteration in lymph node structure (Krivit and Good, 1959; Root and Speicher, 1963).

Whatever the basic significance of this reticulo-endothelial proliferation in Wiskott-Aldrich syndrome, the histological features in the brain in our case were clearly those of a malignant reticulosis. These features included cells with bizarre atypical nuclei sometimes resembling Reed-Sternberg cells, numerous mitotic figures, and necrosis and haemorrhage in the infiltrated areas.

Neoplasms of the reticuloendothelial system of the brain have been described under a variety of titles, including reticulum cell sarcoma (Burststein, Kernohan, and Uihlein, 1963), perivascular sarcoma (Abbott and Kernohan, 1943), perithelial sarcoma (Hanbery and Dugger, 1954), and microgliomatosis (Miller and Ramsden, 1963; Russell, Marshall, and Smith, 1948). Russell *et al.* (1948) interpreted these tumours as largely composed of cells with the morphological characteristics of microglia, with the more primitive cells arising by dedifferentiation of mature elements. Rubinstein (1964) states, 'the alternative possibility cannot be disregarded, namely that the tumors arise from the more primitive elements, possibly undifferentiated periadventitial reticulum cells, and that the more mature microglial forms may represent their differentiated descendants'. Peison and Voris (1965) believed that the tumour cells in their case of primary reticulum cell sarcoma of the brain arose directly from the adventitial cells of intracerebral blood vessels. There is general agreement (Miller and Ramsden, 1963; Peison and Voris, 1965; Russell *et al.*, 1948) that the absence of cytoplasmic staining by the Hortega silver carbonate method distinguishes primitive reticulum cells from mature microglia. In our case, the cellular proliferation was largely restricted to the perivascular areas, and the neoplastic cells did not stain with silver carbonate. They were therefore interpreted as reticulum cells rather than neoplastic microglia.

The brain was involved in 2 of the 5 cases of Wiskott-Aldrich syndrome (Chaptal *et al.*, 1966; Diamond, 1966; Kildeberg, 1963; Pearson *et al.*, 1965; ten Bonsel *et al.*, 1966) in which a malignant reticulosis or a lymphoma was reported. In one case, only a brief summary of the pathological

findings was given; there was a 'malignant growth of abnormal reticulum cells in the intestinal wall and lymph nodes with metastases to the brain' (Kildeberg, 1963). In the second case (ten Bonsel *et al.*, 1966), a 6½-year-old boy with a large mass in the jejunum and numerous well-circumscribed nodules in the cerebral hemispheres, the histological findings in the brain were similar to those observed in our case. Tumour cells formed 'sleeves about small blood vessels'. In both cases the presence of tumour in the brain was interpreted as metastatic. By contrast, in our case a malignant reticulosis occurred primarily in the central nervous system and no neoplastic changes were found elsewhere in the body.

While the pathogenesis of Wiskott-Aldrich syndrome is not known, the concomitance of recurrent infections, depressed or absent delayed (cellular) immunity (Cooper *et al.*, 1964a), an abnormal profile of serum immunoglobulin levels, in particular a low IgM (Cooper *et al.*, 1964b), a frequently hypoplastic thymus (Wolff, 1967), and the lymphoid depletion and histiocytic proliferation commonly found in the lymph nodes (Krivit and Good, 1959) attests to the presence of immunological impairment. This patient showed all of these features at some stage of his disease. If recurrent infection is an index of an immunological impairment, this was present by the age of 5 weeks. At 3 months, a chest x-ray showed a normal thymic shadow, but the thymus was not found at necropsy. At 2 years, a vesicating dose of dinitrofluorobenzene failed to sensitize, showing a depression of cellular immunity. At the same time, he had a normal antibody response to typhoid-paratyphoid vaccine, and, as shown in the Table,

TABLE
Autoimmune Response to Infection in Patient with Wiskott-Aldrich Syndrome

Age (yr.)	Clinical Status	Ig G (mg./100 ml.)	Ig A (mg./100 ml.)	Ig M (mg./100 ml.)
2 3/12	6 months before onset of pseudomonas meningitis	949	256	18
3	3 months after onset of pseudomonas meningitis	1450	740	44
3 1/12	2 days before death	1960	790	76

his previously low IgM level rose to normal during the terminal infection, suggesting an adequate antibody response.

In animals, a viral aetiology has been proposed for reticuloendothelioses in mice (Gross, 1954), cattle (Bendixen, 1966), cats (Jarrett *et al.*, 1964), and fowl (Theilen, Zeigel, and Twiehaus, 1966). If a virus is also operative in the human form of this disease, it is reasonable to expect an increased incidence under conditions of impaired immunity, and this has been shown: lymphoreticular malignancies have been reported to occur at an unusually high frequency in sex-linked hypo- γ -globulinaemia (Bruton's type) (Page, Hansen, and Good, 1963), ataxia telangiectasia (Peterson, Kelly, and Good, 1964), primary acquired hypo- γ -globulinaemia (Peterson, Cooper, and Good, 1965), and macroglobulinaemia (Edgar and Dutcher, 1961).

Wiskott-Aldrich syndrome differs from these antibody deficiency diseases, but shares with them an impaired immunity, a history of recurrent infections, and an increased incidence of lymphoreticular malignancy. These associations suggest that infection may play an aetiological role in this form of malignancy but do not exclude the possibilities that both the immunopathy and the malignancy stem from the same basic defect, or that the latency period for the development of the malignancy may be manifested by various forms of immunological deficiency. Even if infection has a causal relation to the malignancy, it remains necessary to distinguish between infection by a specific infective oncogenic agent, and intense chronic stimulation of the reticuloendothelial system by a variety of infectious organisms.

Summary

A patient with Wiskott-Aldrich syndrome is described in whom a primary malignant reticuloendotheliosis, limited to the central nervous system, developed after an episode of chronic bacterial meningoencephalitis. The occurrence of malignant reticuloendotheliosis in this disorder is probably not uncommon.

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Errata

Levin *et al.* : Hyperammonaemia: a deficiency of liver ornithine transcarbamylase. Occurrence in a mother and child. (1969) **44**, p. 157, Table III, line 7—the concentration of alanine should be 1.7 mg./100 ml. (*not* 0.06 mg.).

Levin *et al.* : Hyperammonaemia: a variant type of deficiency of liver ornithine transcarbamylase. (1969) **44**, p. 165, Table III, line 5, column 4—the level of arginine should be 0.79 mg./100 ml. (*not* 0.29 mg.).