TWO MALAYSIAN CHINESE MALE CHILDREN WITH THE WISKOTT-ALDRICH SYNDROME

Y. H. Tong
D. Sinniah
R. Murugasu
J. C. White

**Department of Paediatrics,
University of Malaya,
Kuala Lumpur, Malaysia.**

Y. H. Tong, MBBS, FAAP
Lecturer

D. Sinniah, MA, MD, MRCPI, FRACP, DCH
Assoc Professor

**Department of Pathology,
University of Malaya**

R Murugasu, MBBS, MRC Path
Lecturer

J.C. White, MD, FRC Path
Assoc Prof

Present Address

Y.H. Thong
**University Department of Paediatrics,
Adelaide Children Hospital
North Adelaide, 5006 Australia**

R. Murugasu
**Staff Specialist Office, Royal Newcastle Hospital
Newcastle, N.S.W. 2300, Australia**

K.C. White
**Department of Haematology,
St. Bartholomew's Hospital Medical College
West Smithfield, London, EC1A 7BE**

**Request for reprints to
D. Sinniah**

SYNOPSIS

Two Malaysian Chinese male children are described with Wiskott-Aldrich syndrome, which has rarely been reported in the East. Classical features were found, with bleeding and infections, low titres of isohaemagglutinins and IgM, but variable IgG and IgA. The immune response was broadly disturbed. Survival of one child was sufficiently long for a lymphoreticular malignancy or appear.

INTRODUCTION

The sex-linked Wiskott-Aldrich syndrome, with repeated bleeding, eczema and infective episodes, has been described mainly in Caucasian families, although reported in a black American family (Woff and Bertucio, 1957) and in a child from Singapore (Paul, 1975). Two Malaysian male children with this condition are described here.

CASE REPORTS

CASE 1

At age 4 months Y.H.K., a male infant was seen at the University Hospital, Kuala Lumpur, with haematemesis, purpura, eczema and bilateral otitis media. There was no family history of significance.

LABORATORY INVESTIGATIONS

The blood count revealed haemoglobin 9.0 g/dl, reticulocytes 3.5%, platelets $65 \times 10^9/l$ and small in size; WBC $11 \times 10^9/l$ (polymorphs 32%, lymphocytes 55%). Aspirated marrow showed active erythro-and granulopoiesis, low iron stores, few plasma cells and scanty megakaryocytes with granulated cytoplasm but little platelet budding. Platelet aggregation induced by ADP was reduced; fibrinogen was low (0.95g/dl) with presence of degradation products and cryofibrinogen.

Blood group was A (Rhesus positive), with anti-B isohaemagglutinin titre 1 : 4. Serum total proteins was 65g/l, albumin 32g/l and globulins 33g/l; paper electrophoretogram was normal but high titres of IgG (1 : 1046) and IgA (1 : 128) and low IgM (1 : 16) levels were obtained by Ouchterlony immunodiffusion. All laboratory tests were normal in the parents and 2 sisters.

He developed bronchpneumonia at age 8 months, salmonella enteritis at 9 months, and died from gastroen-

teritis, pneumonia and pseudomonas septicaemia at 11 months.

MICROSCOPIC FINDINGS AT NECROPSY

The thymus was atrophic (fig. 1A) lymph nodes were deficient in germinal follicles (fig. 2A & B) and cytomegalovirus inclusions were seen in the salivary glands (fig. 1B).

CASE 2

At age 19 days C.H.S. a male infant was admitted with staphylococcal sepsis and gastroenteritis, and again for gastroenteritis at 5 and 17 months. Multiple episodes of epistaxis, haematemesis, purpura, rectal bleeding and eczema required admission at age 2½ years (fig. 3 & 4). All 4 male siblings died in infancy from bleeding and infection, but the parents and 1 female sibling are alive and well.

LABORATORY INVESTIGATIONS

At age 2½ years the haemoglobin was 9.9g/dl, reticulocytes 1.9%, platelets 22 $\times$ 10^9/1 and very small in size; WBC 8 $\times$ 10^9/1 (polymorphs 57%, lymphocytes 37%). Aspirated marrow showed active erythro-and granulopoiesis, low iron stores, occasional plasma cells, and increased megakaryocytes with cytoplasm basophilic or granulated and scanty or absent platelet budding. Over a 3-year period bleeding time was prolonged, platelet adhesiveness and aggregation by ADP was defective, with a wide range of fibronogen values (1.95 — 7.25g/l) and fibrinolysis varying between activated and suppressed.

Blood group was B (Rhesus positive), with anti-A titre 1 : 1 to 2. Serum total proteins was 62g/l, albumin 32g/l and globulins 29g/l, with a rising immunoglobulin zone in paper electrophoretograms; by Ouchterlony immunodiffusion, IgG titre rose from 1 : 128 to 1 : 1024, with normal IgA (1 : 32 to 64) and low IgM (1 : 4 to 8).

From 2½ to 5 years of age there were 11 more admissions, including (1) pneumonia and staphylococcal septicaemia, when levamisole was given for 5 days without apparent influence on subsequent infections, (2) left mandibular abscess, (3) wound infection and bleeding after herniorrhaphy, treated by fresh blood and platelet transfusion, (4) multiple abscesses. Immunological studies at age 4½ years revealed normal in-vitro lymphocyte response to phytohaemagglutinin, assessed by 3H-thymidine incorporation, but negative skin response to PPD, although BCG was given during infancy. Serum levels of immunoglobulins: IgG 3.40, IgM 1.38 and IgA 1.23g/l. Antibody responses to TAB vaccine were negative, and lymph node biopsy performed 7 days after 2 doses in the thigh showed poor development of germinal follicles (fig. 5A & B).

On final admission at age 5½ years he was emaciated, dehydrated, oliguric, with petechiae and bilateral aural discharge. The condition deteriorated further with chest infection, abdominal pain and signs of peritonitis before death.

NECROPSY FINDINGS

Peritonitis was present from perforation of one of multiple tumour masses in small intestine and liver. The tumour structure was that of non-Hodgkin's lymphoma. Broncho-penumonia, bilateral otitis media, candida oesophagitis and necrotising colitis were found, as well as chronic persistent hepatitis with hepatitis B surface antigen demonstrable in hepatocyte cytoplasm. There was lymphocyte and plasma-cell depletion of lymph nodes and spleen, and atrophic thymus. Sub-dural and intracerebral haemorrhages, cutaneous petechiae and ecchymoses were present.

DISCUSSION

Both cases illustrate the typical progression of combined bleeding tendency and susceptibility to repeated infection found in Wiskott-Aldrich syndrome (Murphy, 1972), with the emergence of a lymphoreticular malignancy in the child surviving much longer for 5½ years (Bensel *et al,* 1966).

Platelets were abnormal in structure and function, with defective budding from the marrow megakaryocytes in both children (Pearson *et al,* 1965), although these were reduced in one and increased in the other case. Failure of oxidative phosphorylation regulation has been suggested by Kuramoto *et al* (1970) as a possible link between the defective platelets and disturbed macrophage function in the immune response in this sex-linked disorder.

There was a broadly-based disturbance of immunity with multiple bacterial infections suggesting disturbed humoral responses (Blaese *et al,* 1968), and presence of defective cell-mediated immunity in view of the abnormal lymph node architecture and occurrence of viral and fungal infections. However, negative response to PPD encountered in Case 2 is not uncommon in Malaysian children receiving BCG in early infancy. Levamisole therapy was attempted as a means of immune potentiation in Case 2 (Lieberman and Hsu, 1976), but without apparent effect on occurrence and course of subsequent infections.

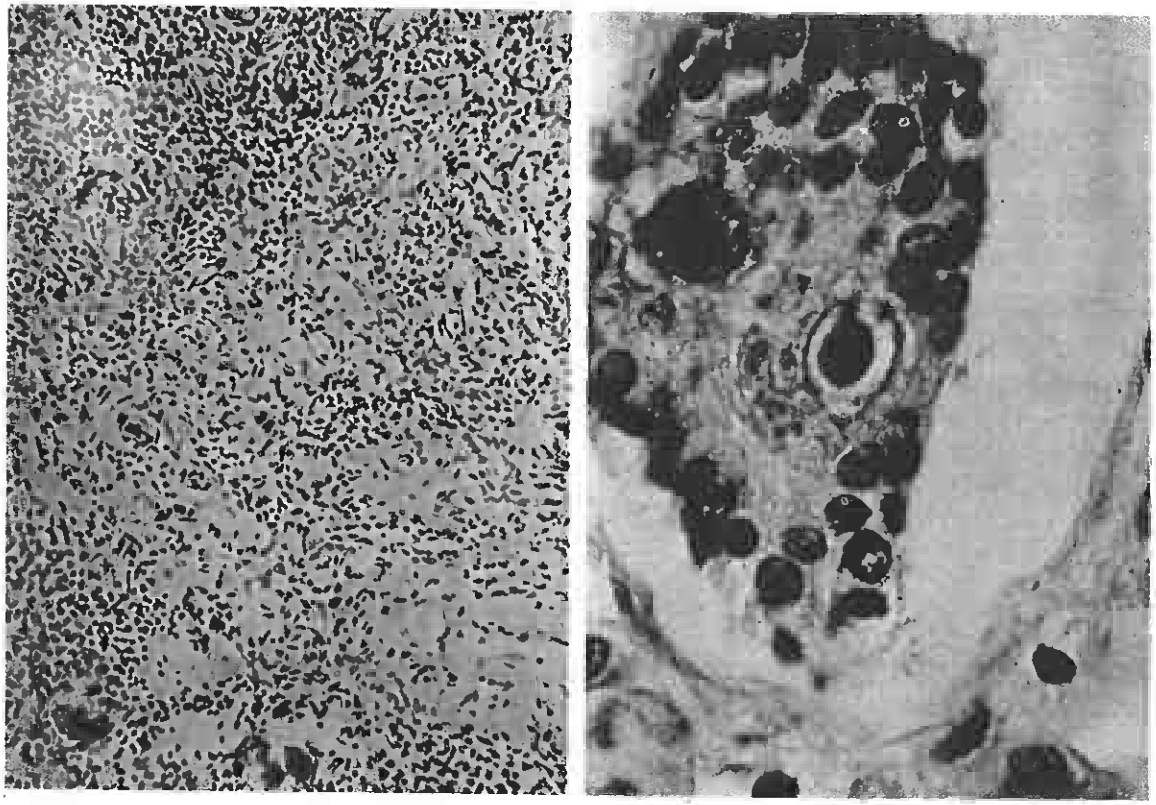


Fig. 1A Atrophic thymus with small, calcified Hassall's corpuscles.
1B Cytomegalovirus inclusion body in salivary gland.

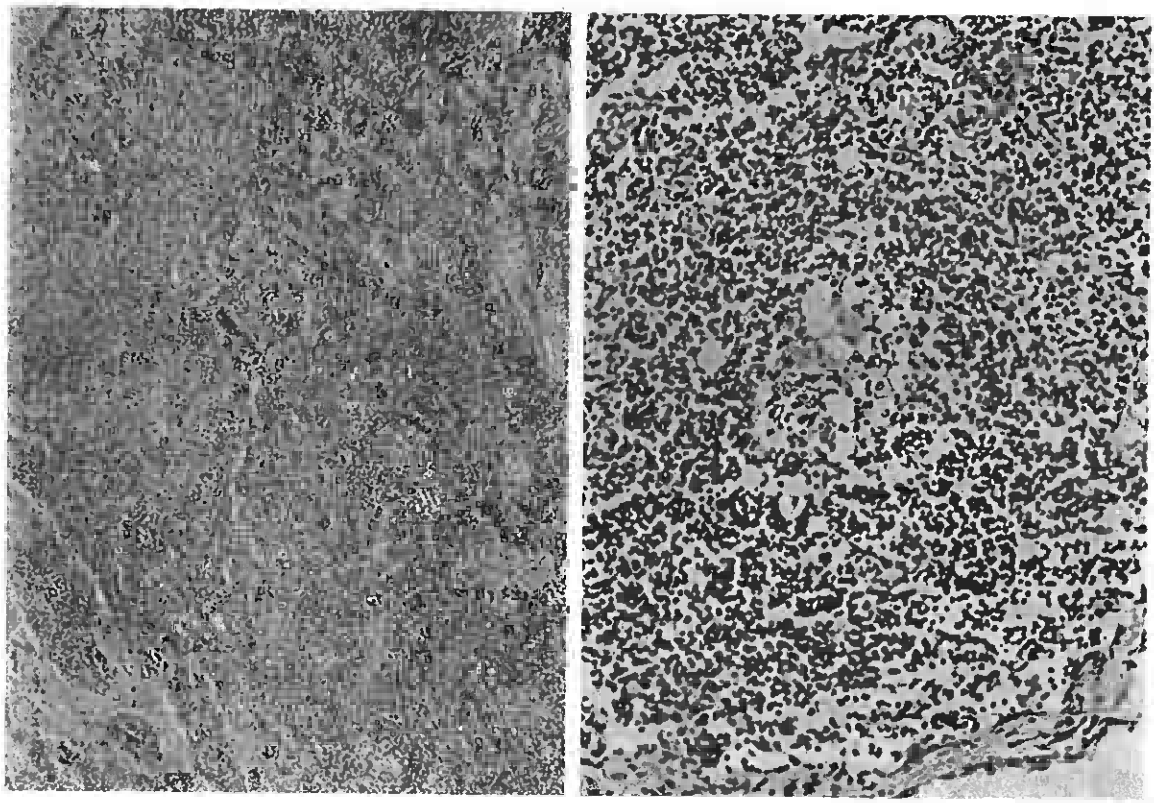


Fig. 2A Low power view showing general hypocellularity.
2B Lymph node with poorly developed germinal follicles in cortex.

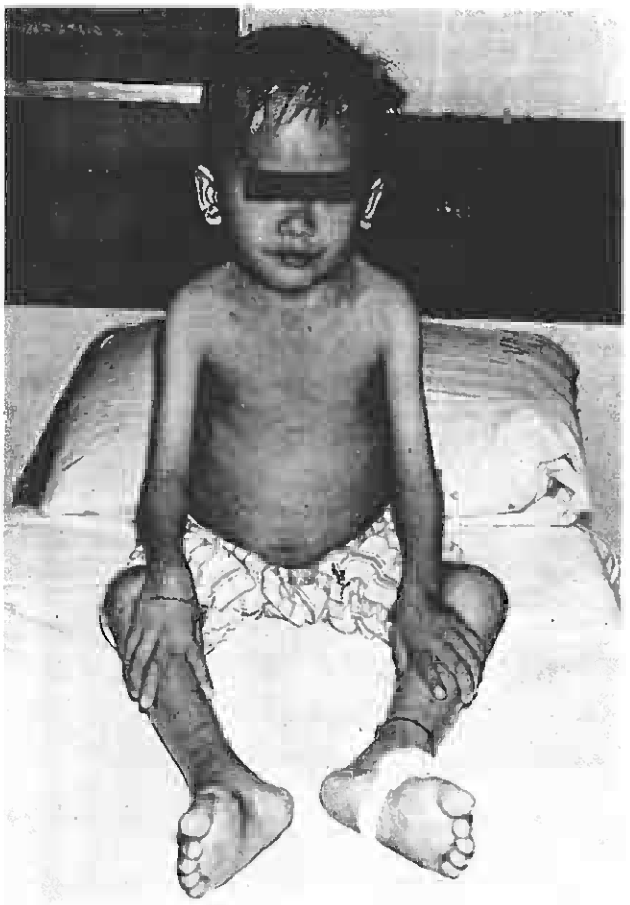


Fig. 3 Patient C. H. S.

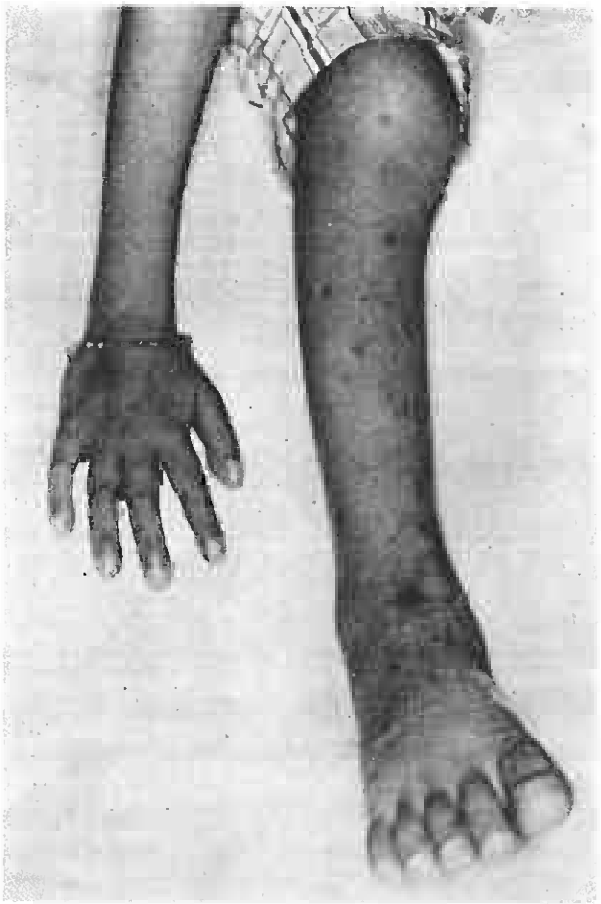
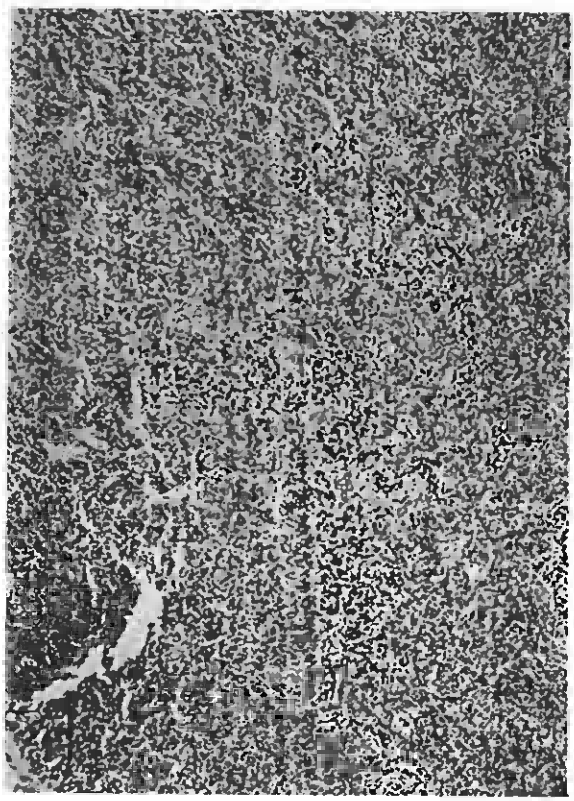


Fig. 4 Patient C. H. S. showing petechiae on leg



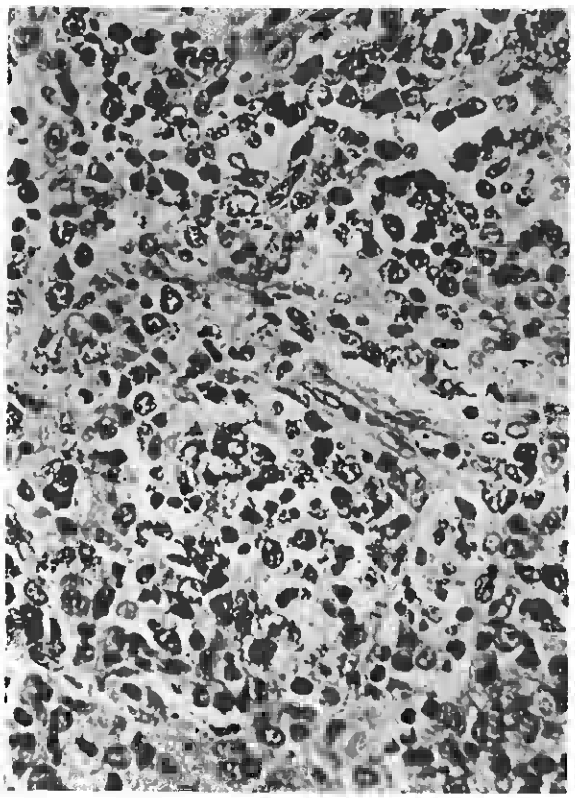


Fig. 5A Lymph node hiopsy following antigenic stimulation: germinal centres.
5B Higher power view showing poorly developed hypocellular appearance.

ACKNOWLEDGEMENTS

We are indebted to Dr. Greg Binns, Mrs. Barbara Wood, and members of the Photography Department, Adelaide Children's Hospital, for assistance.

REFERENCES

1. Blaese, R.M., Strober, W., Brown, R.S., and Waldman, T.A.: The Wiskott-Aldrich syndrome. A disorder with a possible defect in antigen processing or recognition. Lancet, 1 : 1056, 1968.
2. Kuramoto, A., Steiner, M.D., and Baldini, M.G.: Lack of platelet response to stimulation in the Wiskott-Aldrich Syndrome. New Engl. J. Med., 282 : 475, 1968.
3. Lieberman, R., and HSU, M : Levamisole-mediated restoration of cellular immunity in peripheral blood lymphocytes of patients with immunodeficiency disease. Clin. Immunol. Immunopath., 5 : 142, 1976.
4. Murphy, S : Hereditary thrombocytopenia. Clin. Haemat., 1 (2) : 359, 1972.
5. Paul, F.M. : Some cases of immunoglobulin abnormalities in Singapore children. Proc. Tenth Singapore-Malaysia Congr. Med., 1975, pp. 147 — 154.
6. Pearson, H.A., Shulman, R.N., Oski, F.A., and Etizman, D.V.: Platelet survival in Wiskott-Aldrich Syndrome. J. Pediat., 68 : 754, 1966.
7. Bensel, R.W., Stadlan, E.M., and Krivit, W : The development of malignancy in the course of the Aldrich syndrome. J. Pediat., 68 : 761, 1966.
8. Wolff, J.A. and Bertucio, M : A sex-linked genetic syndrome in a Negro family manifested by thromobocytopenia, eczema, bloody diarrhoea, recurrent infection, anaemia and epistaxis. A.M.A. J. Dis. Child., 93 : 74, 1957.