STAGE IV-S NEUROBLASTOMA A REVIEW FROM THE UNIVERSITY HOSPITAL, KUALA LUMPUR

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SYNOPSIS

A review of 20 cases of neuroblastoma at the University Hospital, Kuala Lumpur from 1967 to 1980 reveals six infants aged 2 to 13 months with stage IV-S disease, associated with an unusually good prognosis. Four of the six patients presented with hepatomegaly, one had skin nodules and another paresis of the lower limbs. The primary tumour was located infra-diaphragmatically in all cases, four had disease in the bone marrow but none had radiological evidence of bone involvement. Although not systematic, with limited treatment of low dose radiation and mild chemotherapy, four patients are alive and well, one absconded and one died of septicaemia.

It is important to define this special category as an unexpectedly good survival is possible with minimal therapy. Death is more likely to result from over-zealous treatment than from the disease itself.

INTRODUCTION

Although the prognosis of widespread neuroblastoma is generally poor, a special category of children who have an unusually good outlook has been recognised (1, 2, 3). Such children have been classified as stage IV-S in the staging criteria proposed by Evans et al (4). It is important to recognise this group of patients as little or no treatment may be necessary.

We review here our experience of all children with stage IV-S disease diagnosed at the University Hospital, Kuala Lumpur to define the epidemiological, clinical and pathological characteristics and outcome in these cases.

PATIENTS AND METHODS

Twenty patients with neuroblastoma were admitted to the University Hospital, during the period 1967 through March 1980, of whom six fall within the category of stage IV-S as defined by Evans et al (4); ie. patients with tumour confined to the organ or structure of origin or tumour extending in continuity beyond the organ or structure of origin but not crossing the midline (regional lymph nodes on the ipsilateral side may be involved) and who have remote disease confined to one or more of the following sites: liver, skin or bone marrow without radiographic evidence of bone metastases on complete skeletal survey (Table I). The main clinical and pathological features of these six cases and are summarised (Table II).

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Table I Staging system for neuroblastoma

Stage	
I	Tumour limited to organ of origin
II	Regional spread not crossing midline
III	Tumour crossing the midline or metastatic tumour in contra-lateral nodes
IV	Patients with haematogenous or distant metastases
IV-S	Patients who would otherwise be stage I or II but who have metastases limited to liver and/or skin and/or bone marrow without radiographic evidence of bone metastases

RESULTS

The 6 cases include 4 Chinese, 1 Malay, and 1 Indian of whom 4 were males and 2 females with an age range of 2 to 13 months. All had elevated levels of vaniyl mandelic acid in the urine.

Clinical Features

The commonest presenting symptoms were abdominal distension in 4 cases, skin nodules in one and weakness of the lower limb in another; other symptoms included weight loss, pallor and fever.

Details of the tumour

Biopsies or resections of the primary tumours were available for review in 5 of the 6 cases. The site of primary tumour was identified either at operation or from the results of investigations which included excretory urography and skeletal survey. All were infra-diaphragmatic; 3 were in the right adrenal, 1 in the left adrenal, 1 in the retroperitoneum and 1 extradurally in the spine. The liver was enlarged 2 to 12 cm in 5 patients but liver scan revealed "cold areas" in only 2 cases. Needle biopsy of the liver confirmed the diagnosis in 2 cases (Fig. 1) and skin biopsy in another. Bone marrow aspiration revealed malignant cells in 4 cases (clumping in 2 cases) which were differentiated from leukaemic cells morphologically and cytochemically (Fig. 2).

Treatment and Survival

The details of treatment and survival are summarised in Table III. One patient (no. 4) refused treatment and nothing is known of her subsequent outcome. Two (no. 2 & 3) had partial resection of the tumour, radiotherapy to the liver and limited chemotherapy of whom one succumbed to pseudomonas septicaemia within 3 months of admission and autopsy disclosed no evidence of tumour anywhere while the other child is well and tumour free 5 years later. Complete resection of the tumour was accomplished easily in 2 cases (no. 5 & 6) and they are alive and well 14 months and 12 months later. Another patient (no. 1) received 2 courses of combination chemotherapy followed by 12 doses of weekly vincristine to reduce a very large sized liver which initially prevented access to the primary tumour which was later removed completely at a second operation (Fig. 3).

Of the 6 cases of stage IV-S neuroblastoma, 4 are alive and well 1 to 6 years later, one died of septicaemia while the outcome of the other who absconded is not known.

DISCUSSION

Despite the increased in the frequency and duration of

Table II Clinical and pathological features in 6 cases of stage IV-S patients

Case No.	Age	Primary Site	Distant Disease			
			Liver	Skin	Marrow	Other
1	2 (mo)	L-adrenal size 2x2x2 (cm) Wt. 5.4 kg	+ (Biopsy)	0	+	0
2	4 (mo)	R-adrenal with infiltration of R kidney, para-aortic nodes and psoas on ipsilat side	2 cm	0	+	0
3	11 (mo)	Retroperitoneal 2x1x1 (cm)	+ (needle biopsy) (scan +)	0	+	0
4	8 (mo)	R. Adrenal	Cold Areas on scan	0	0	0
5	13 (mo)	R. Adrenal 6x4x5 (cm) Maturity to ganglioneuroma	1 cm (enlarged in scan)	+	0	0
6	7 (mo)	Extradural spine T12-12 size 1 cm	1½ cm (enlarged in scan)	0	+ (clump)	0

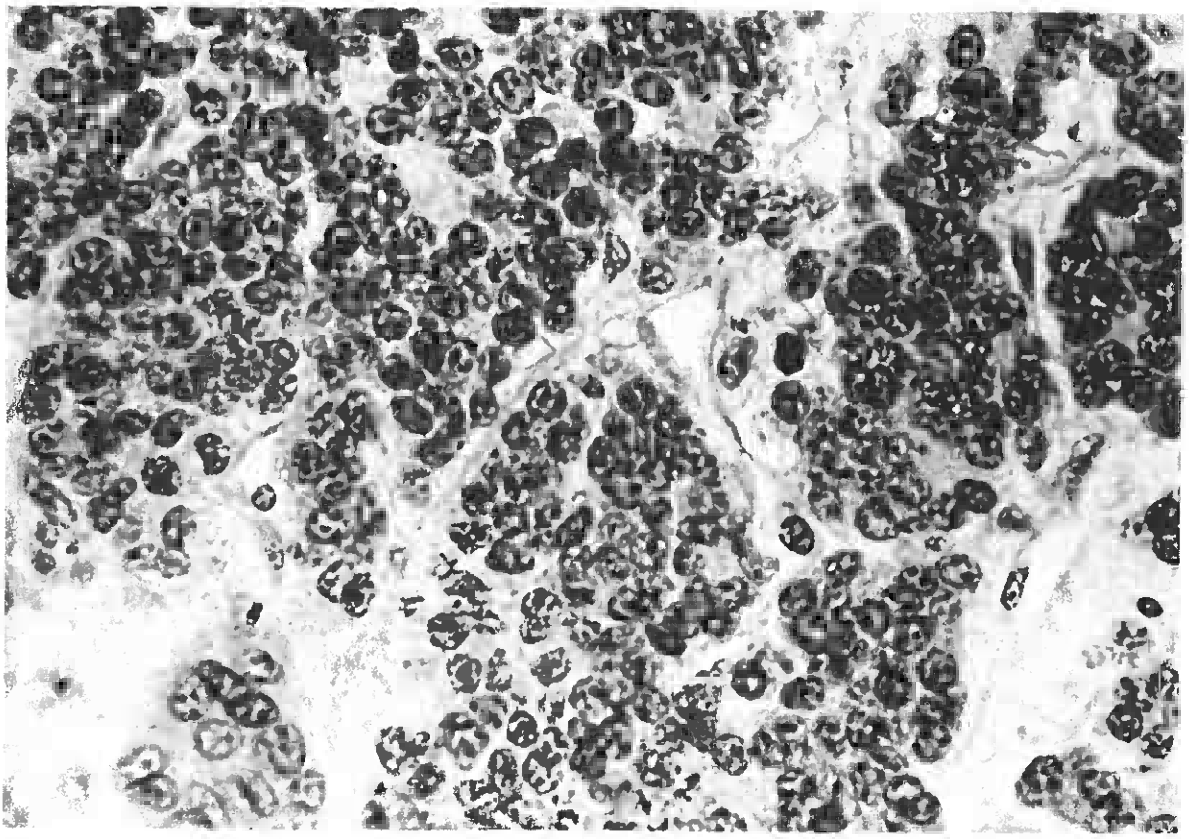

Figure 1 Liver biopsy showing metastatic neuroblastoma (H & E)

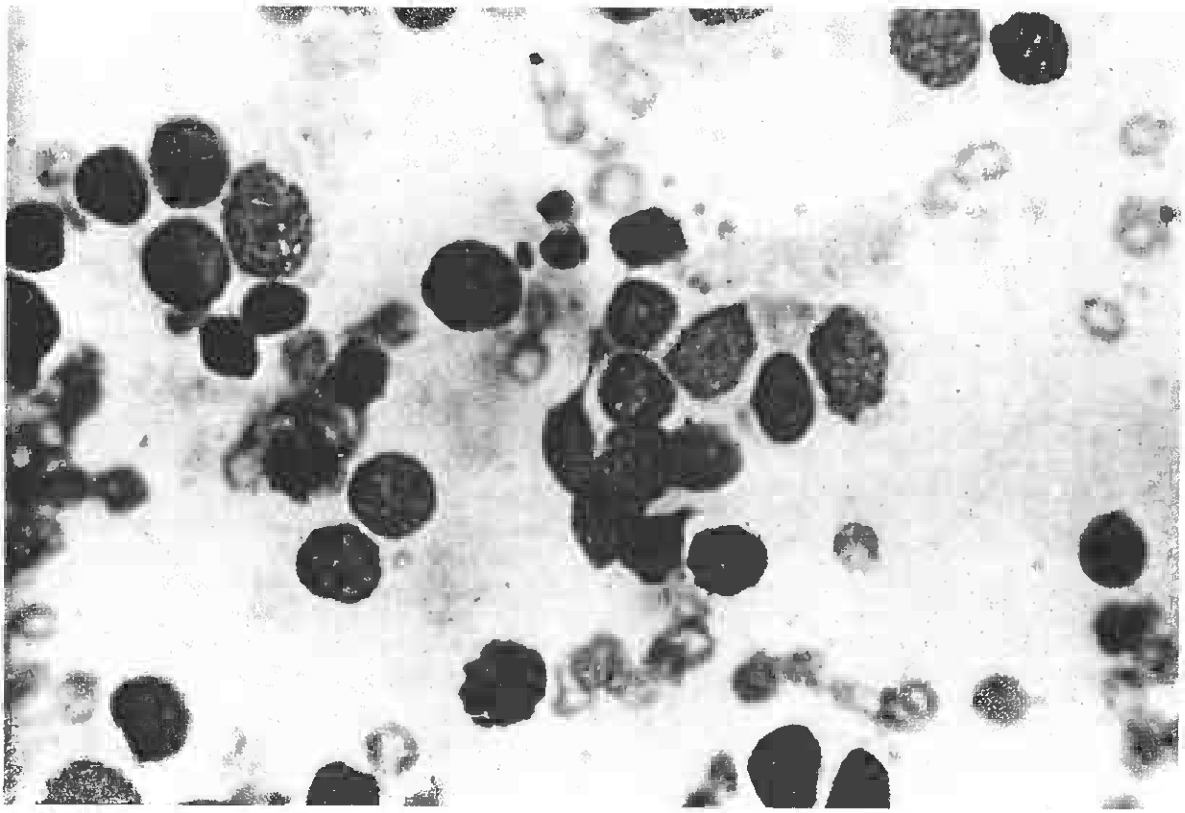

Figure 2 Bone marrow examination revealing heavy infiltration by neuroblastoma cells which are PAS and peroxidase negative

Table III Outcome of treatment in 6 cases of stage IV-S neuroblastoma

Case No.	Year	Treatment			Outcome
		Surgical excision	Radiotherapy	Chemotherapy	
1	1974	Complete	0	Pre-op. VCR, CPA + VBL for 2 wks. Post-op. VCR x 12 doses	A + W at 6 yrs
2	1975	Partial	+	VCR, CPA + PNSL - 2 courses	Died at 3 mos. of septicaemia. PM - NAD
3	1975	Partial	+	VCR, CPA + ADM 2 wkly x 6 courses	A + W at 5 yrs.
4	1976	0	0	0	Absconded.
5	1979	Complete	0	0	A + W at 14 mos.
6	1980	Complete	0	VCR x 12 doses	A + W at 1 yr.

A + W = alive and well; VCR = vincristine; ADM = adriamycin; CPA = cyclophosphamide; PNSL = prednisolone; VBL = vinblastine; PM = post mortem

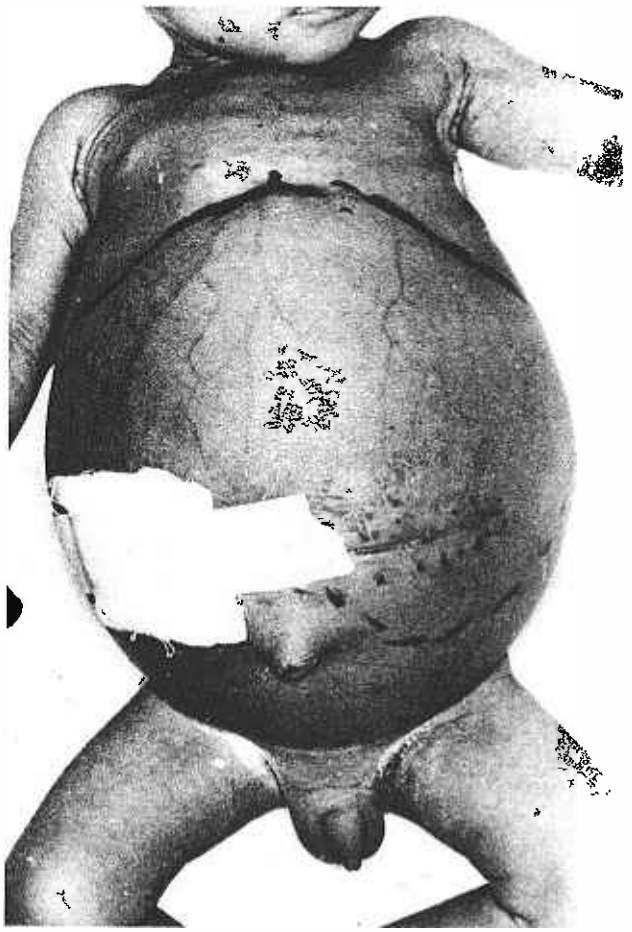

Figure 3 Gross hepatomegaly due to stage IV-S neuroblastoma preventing access to the primary which was later removed completely at a second operation after a course of chemotherapy

remission achieved in children with disseminated neuroblastoma with combination chemotherapy, the 32 per cent 2 year overall survival rate remains the same today as it was prior to the use of these drugs.

Evidence from several series however reveals that stage IV-S neuroblastoma is associated with a surprisingly good prognosis (1, 2). The natural history would appear for the tumour to regress completely or to mature into a ganglioneuroma (6, 7). Death is now more likely to result from over-zealous treatment than from the disease itself. The reason for the spontaneous regression of neuroblastoma which occurs most often in babies, remains speculative but may be related to a unique interaction between the host and the tumour (8). The tumour usually regresses by necrobiosis and maturation to ganglioneuroma is rare (9). Included in our series is a case with multiple skin nodules and a right adrenal neuroblastoma with the histopathological features of a ganglioneuroma (Fig. 4).

The optimal method of treatment is difficult to assess in view of the diversity of the type, dose and duration of chemotherapy and radiotherapy used. Removal of the primary tumour is advocated at some time during the course of the disease since an occasional patient may develop a late local recurrence even though the bulk of the disease has regressed (10, 11). Partial excision of the primary without further treatment of any kind has led to long term survival as in some cases where no treatment has been given (6, 12).

Although four of our patients had bone marrow infiltration, none had X-ray evidence of bone involvement which is an ominous prognostic sign and separates the poor from the good prognosis patients. A grey zone probably exists where heavy marrow involvement presages bone invasion.

Early age and hepatic infiltration have been proposed as the two corner stones on which to rest the special grouping with a good prognosis but tumour can be present in other sites without necessarily worsening the prognosis (9). Not all stage IV-S children survive; death results more usually from comprehensive phenomena or haematologic compli-

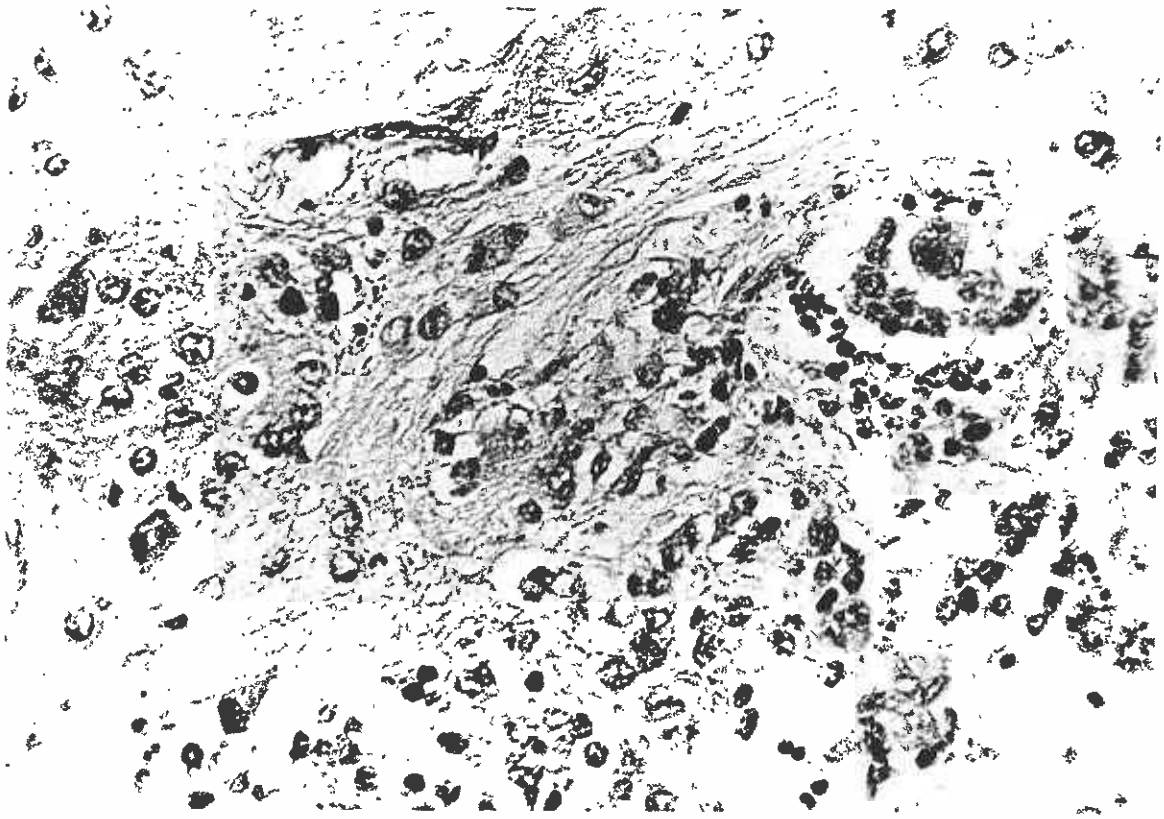

Figure 4 Stage IV-S neuroblastoma with pathological features of a maturing ganglioneuroma

cations rather than from destruction of vital organs. Treatment should be gentle enough to initiate regression of tumour which then should disappear without need for additional therapy.

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