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RETICULUM CELL SARCOMA IN CHILDREN

LUIS BORELLA, M.D.*

Memorial (NYC)

PRIMARY MALIGNANT TUMORS OF LYMPHOID origin are usually considered to be fatal in children; in addition, these diseases usually have a more rapid and difficult course in the younger age group than that seen in adults. The problems of diagnosis, treatment, and prognosis as related to morphology are obscured by the multiple classifications in different institutions; attempts have been made to achieve a standard classification applicable to all cases, but these have not been successful. One pathological diagnosis that has been constant in most classifications is that of reticulum cell sarcoma (RCS) and studies of prognosis indicate that this is the most malignant of all the lymphoid tumors. Due to the paucity of studies limited specifically to RCS in children, this study of 45 cases is presented in the hope that it will provide a better understanding of the clinical picture, treatment, and prognosis, as well as an increased awareness of this specific disease process.

CASE MATERIAL

This series of 45 cases of RCS is composed of children with that diagnosis admitted to the Pediatric Service of Memorial Hospital for Cancer and Allied Diseases from 1933 through 1961. Some have been previously reported in general studies of lymphosarcoma in children.[4, 6, 7, 8] The group includes 35 male and 10 female patients: the youngest at the time of diagnosis was 15 months of age and the oldest 14 years, with a mean age of 7.4 years. The composition of the group is shown in Table 1.

Cases of RCS of bone have been excluded because of site of origin. This may be an oversight because of similarity of progression of disease, brit all cases included have arisen in lymphoid tissue. Tissue biopsy and/or post-mortem examination established the histological diagnosis in all cases. Subsequent course, both as inpatients and outpatients, has been documented by members of the staff of the Hospital.

Clinical Manifestations. Vague symptoms such as low grade fever, anorexia, generalized weakness, and loss of weight were the usual

TABLE 1

AGE AT ONSET, SEX, RACE, AND ANATOMIC SITE OF TUMOR IN 45 PATIENTS WITH RETICULUM CELL SARCOMA

Case no.	Pt. init.	Pt. age, yr.	Pt. sex	Pt. race	Anatomic site tumor
1	S.M.	1¼	M	W	Cervical
2	C.A.	2	F	W	Cervical
3	B.S.	2	M	W	Nasopharyngeal
4	B.M.	2	M	W	Nasopharyngeal
5	G.R.	3	M	W	Mediastinal
6	S.B.	3	M	W	Subcutaneous
7	S.M.	3	F	C	Cervical
8	T.B.	3	M	W	Abdominal
9	C.P.	3	F	W	Abdominal
10	C.S.	3½	M	W	Abdominal
11	L.J.	4	M	W	Abdominal
12	v.11.	4	M	W	Abdominal
13	R.L.	4½	M	W	Abdominal
14	B.A.	4½	M	W	Generalized
15	J.C.	5½	M	W	Abdominal
16	B.J.	6	M	W	Subcutaneous
17	O.T.	6	F	W	Generalized
18	W.E.	6½	M	W	Cervical
19	B.J.	6½	F	W	Mediastinal
20	K.T.	7	M	W	Abdominal
21	B.T.	7	F	W	Cervical
22	S.J.	8	M	W	Nasopharyngeal
23	11.11.	8	M	W	Abdominal
24	R.G.	8	M	W	Nasopharyngeal
25	F.B.	8	F	W	Cervical
26	H.M.	8	M	W	Abdominal
27	H.W.	8	M	W	Cervical
28	M.B.	9	M	W	Generalized
29	B.D.	9	M	W	Cervical
30	L.L.	9	M	W	Abdominal
31	M.A.	9	hl	W	Abdominal
32	M.D.	9½	F	C	Cervical
33	E.L.	10	M	W	Subcutaneous
34	M.M.	10	M	W	Nasopharyngeal
35	S.L.	10	M	W	Cervical
36	T.M.	11	F	W	Abdominal
37	M.J.	11	M	W	Nasopharyngeal
38	W.M.	11	M	W	Nasopharyngeal
39	W.F.	12	F	W	Cervical
40	L.A.	13	M	W	Generalized
41	G.R.	13	M	W	Subcutaneous
42	M.L.	13	M	W	Abdominal
43	C.D.	13	M	W	Nasopharyngeal
44	M.M.	14	M	W	Abdominal
45	D.R.	14	M	W	Cervical

From the Department of Pediatrics, Memorial Hospital for Cancer and Allied Diseases, 444 E. 68th St., New York 21, N.Y.

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*Present address: Department of Immunology, St. Jude Hospital, Memphis, Tenn.

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ymptoms noted initially. Anemia and/or er manifestations of bleeding were not Seen rly in the disease. In addition to the afotc-entioned vague symptoms, 6 major classifi-ations of symptoms, with or without physical ign were apparent.

Abdominal. This was the commonest form of onset; 15 children (33.3%) presented with dominal pain; 10 had, in association, a mass the abdomen. This mass was usually pal-able, but the possible diagnosis of acute ap-endicitis was the presenting complaint in 3. addition, 4 children developed acute in-ussusception necessitating surgical interven-ion (case 15).

Cervical Adenopathy. Enlargement of 1 or ore cervical lymph nodes, in tlie absence generalized adenopathy, was tlie primary omplaint in 12 (25.6%). No specific abnor-ality of clinical appearance suggested tlic iagnosis, which was made only after biopsy.

Nasopharyngeal Symptoms. The appearance nasopharyngeal mays was usually pre-ded by rhinorrhea, obstructive breathing, nd a "persistent cold." These symptoms were nt for a variable period of time prior io scovery of the mass, and this clinical picture s seen in 8 (17.7%) of the children. As one ould expect, a dental root abscess was tlic itial diagnos s in 2 of tlie children.

Generalized Adenopathy. In comparison to lenopathy limited to the cervical area alonr, 8.8%) presented with enlargement of nodes ll areas

Subcutaneous Nodules. The presence of a subcutaneous mass was the presenting prob-lem in 4 (8.87,) children; all had accompany-ing regional adenopathy.

Mediastinal Mass. The continuing presence of a cough associated with weight loss led to roentgenographic examination of the chest, which demonstrated mediastinal enlargement. This presentation was seen in 2 (4.4%) of the 45 children.

These clinical patterns are relatively non-specific in most instances, and it is again em-phasized that tissue diagnosis is necessary. Figure 1 illustrates the relative incidence of involvement of various tissues. In 8 (17.7%) of these children, the disease remained local-ized to tlic site of origin (and initial diagnosis), but the majority had generalized extension of tlic tumor process. Hepatomegaly was a find-ing in 27 (60%) of the children at sonie time during the course of tlic disease, usually late; in contrast, only 17 (37.7%) had clinically documented splenomegaly.

Urinary tract involvement was another fre-quent complication. Intrinsic disease, later demonstrated to be bilateral at postmortem examination, was seen as frequently as was extrinsic disease, secondary to compression from abdominal or retroperitoneal masses. The major difference was that the extrinsic form was most frequently unilateral with secondary hyclronephtosis on the affected side. The kid-ney involvement was of clinical significance in 19 (42%) of tlie children.

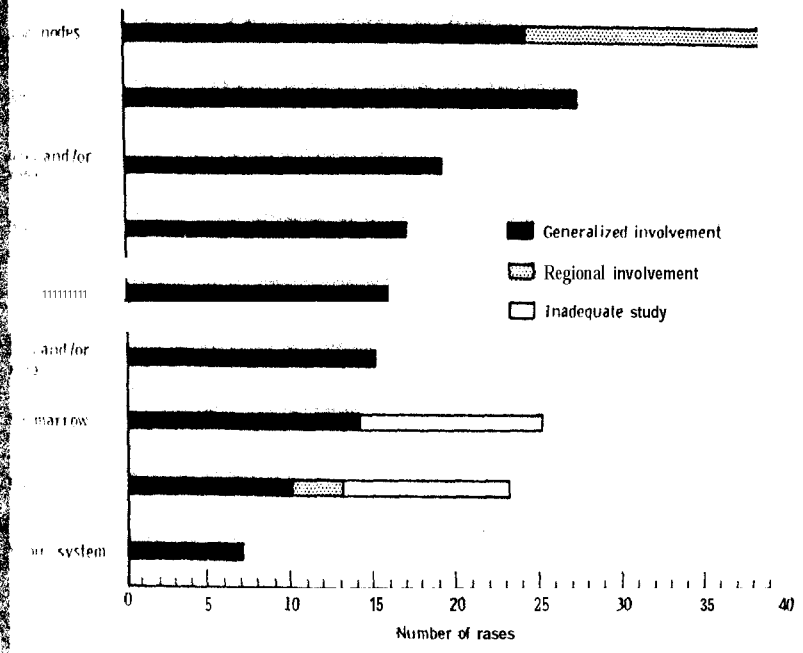

FIG. 1. Systems involved with disease.

TABLE 2

SURVIVAL AS RELATED TO INITIATION OF THERAPY AFTER DIAGNOSIS

Time from onset dis. to treat.	Survival, mo. 0-6	6-12	12-24	24-60	>60	Tot. no. pt.*
0-15 day	1	0	0	0	1	2
15-30 day	9	1	2	2	3	17
1-2 mo.	5	3	0	0	2	10
2-3 mo.	2	1	1	0	1	5
3-6 mo.	0	3	2	0	0	5
6-9 mo.	0	1	1	0	0	2
9-12 mo.	0	0	0	2	0	2
>12 mo.	0	0	0	0	0	0
TOTAL	17	9	6	4	7	43

*Two patients have inadequate follow-up.

The leukemic phase of RCS is assuming a much more important role than previously recognized; 14 of 34 (11 patients did not have bone marrow examination) of the children developed bone marrow changes compatible with a diagnosis of acute leukemia. The time from onset of symptoms to the appearance of leukemic changes in the bone marrow and peripheral blood ranged from 1 to 11 months with a mean of 3.9 months; survival, after leukemic conversion occurred, averaged 2.2 months.

Hematological and other data for these cases are in preparation for subsequent publication.

Mediastinal and bone involvement are the other frequently occurring clinical problems. Mediastinal disease, present in 16 (35.5%), was usually found only by roentgenogram; clinical symptoms necessitating emergency therapy early in the disease did not occur. A superior vena caval syndrome (cyanosis, dyspnea, edema of upper part of body, and venous engorgement) occurred in only 1 patient; prompt relief was obtained with the combination of radiotherapy and nitrogen mustard; 13 (28.8%) children had osteolytic bone lesions—usually generalized; 3 had localized areas of bone involvement; all of these occurred subsequent to origin in a lymphoid site. All children did not have bone surveys, so this figure is not accurate. There was no absolute correlation between bone lesions and bone marrow involvement.

Neurological symptoms were noted in 7 (15.5%) of the children. These were both peripheral nerve and central nervous, related to either meningeal or cortex invasion. This complication is illustrated by case 28 and will be discussed later.

TREATMENT

Therapy was instituted in 70% of the cases within 2 months after the onset of symptoms. No correlation between survival and time of institution of therapy after onset of symptoms could be demonstrated; however, as is shown in Table 2, no 5-year survivals were documented in those whose treatment was delayed 3 or more months after the onset of symptoms. Radiotherapy, surgery, and chemotherapy were all used, singly and in combination, with no definite plan. The results are shown in Table 3. Again, no definite conclusions can be derived, the number of patients in each group being too small. It would appear, however, that neither radiotherapy nor chemotherapy alone should be used in RCS; radiotherapy with or without surgery has been considered standard therapy and a transient response may be obtained as illustrated by Fig. 2A, B, and C. The addition of chemotherapy to either surgery or radiotherapy or both has now become standard; the effectiveness of this is yet to be determined. The common mode of therapy in all but 1 of the 5-year survivors is surgery, indicating that if complete excision is possible, this is our best form of therapy. The extent of surgery necessary for control is demonstrated by the point that the procedures done include radical neck dissection, hemicolectomy, ileal resection, partial pneumonectomy, and splenectomy.

As has been shown for other tumors of lymphoid origin, most cases of RCS are sensitive to radiotherapy initially; it is our experience that subsequent development of radioresist

TABLE 3

SURVIVAL AS RELATED TO THERAPY

Therapy	Survival, mo. 0-6	6-12	12-24	24-60	>60	Tot. no. pt.*
Chemother. only	1	3	0	0	0	4
Radiother. only	4	0	1	0	0	5
Surg. only	0	0	0	0	0	0
Rndiother. & chemother.	12	3	5	3	1	24
Surg. & radiother.	0	1	0	1	1	3
Surg. & chemother.	0	1	0	0	3	4
Surg., radiother., & chemother.	0	1	0	0	2	3
TOTAL	17	9	6	4	7	43

*Two patients have inadequate follow-up.

FIG. 2. A, Mass on ... from January 16 to ...

...ce occurs most ... lymphosarcoma ...als have been ...eated with radia... ...usion would be ...ditive rather tha... Comparably, R... ...re resistant tha... ...ailable chemothe... ...ugs evaluated b... ...mercaptopurine, ...e), vincristine, ...cil, and steroids. The effectiveness ...lustrated in the fo...

Case 28. M.B., ...eloped the follow... ...year after the on... ...e eyes, headache, ...ulsions, and, final... ...mination revealed ...ma. The bone m... ...ncture yielded a ...er cu. mm., all m... ...otein was 280 mg ...herapy of 4 doses ...25 mg. per kg. ... ...diotherapy to th... ...mid-plane tissue ...as instituted. Afte... ...o neurological sym... ...ere within normal ...y showed marked ...ed 2 months late... ...ma with no recu... ...us system disease.

This approach ...

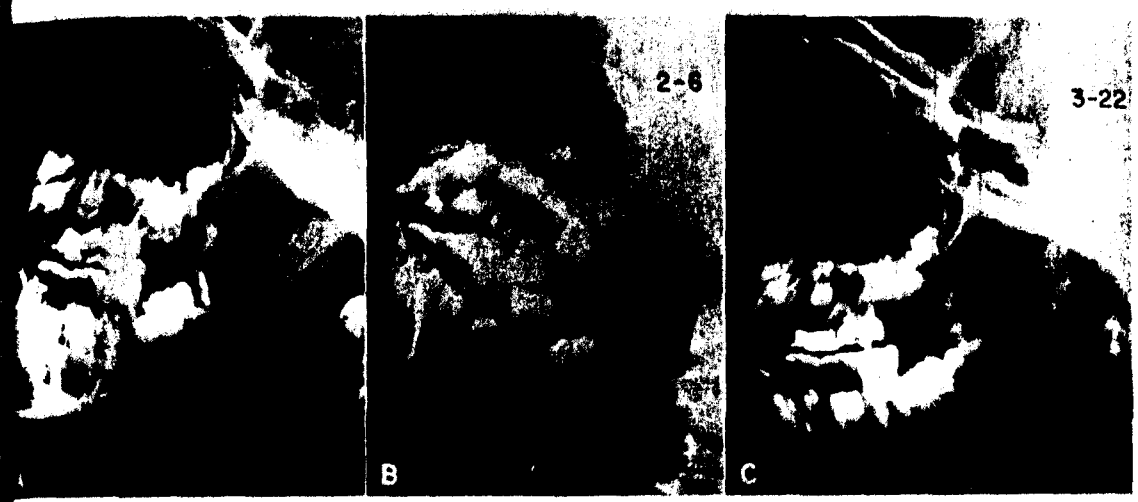

FIG. 2. A, Mass on roentgenogram at time of diagnosis. B, Post-treatment roentgenogram taken after treatment from January 16 to February 3 with a 2,536-r mid-plane tumor dose. C, Roentgenogram showing recurrence.

nce occurs more quickly in this group than lymphosarcoma or other tumors. No survivals have been documented in the group eated with radiotherapy alone, and the conusion would be that radiotherapy should be dditive rather than the only mode of therapy. Comparably, RCS has been shown to be one resistant than the other lymphomas to ailable chemotherapeutic agents. Among the ugs evaluated have been nitrogen mustard, mercaptopurine, amethopterin (Methotrexe), vincristine, cyclophosphamide, chloramcil, and steroids.

The effectiveness of combined therapy is lustrated in the following case.

Case 28. M.B., a 9-year-old white boy, deloped the following neurological symptoms year after the onset of the disease: pain over e eyes, headache, blindness, generalized conulsions, and, finally, coma. Retinoscopic exmination revealed 4 plus bilateral papilleema. The bone marrow was normal. Lumbar uncture yielded a spinal fluid with 5,000 cells r cu. mm., all mononuclear leukocytes; the otein was 280 mg.; and glucose 5 mg. Chemherapy of 4 doses of intrathecal Methotrexate .25 mg. per kg. per dose every 5 days) and diotherapy to the whole brain and orbit mid-plane tissue dose of 1,091 r over 12 days) as instituted. After 20 days, the patient had neurological symptoms; spinal fluid studies ere within normal limits, and his visual acuy showed marked improvement. The child ed 2 months later with reticulum cell sarma with no recurrence of the central nervus system disease.

This approach was successful in management of the immediate problem, but no effect was demonstrated on the systemic disease. Similarly, those children developing RCS leukemia responded for short periods of time to folic acid antagonists, 6-mercaptopurine, and steroids. Clinical experience with the newer compounds (cyclophosphamide and vincristine) is too limited and too short to establish any conclusions.

DISCUSSION

Reticulum cell sarcoma is a rare tumor, as are all the lymphosarcomas in children. Any attempt to determine the exact incidence is doomed to failure because of the multiplicity of pathological classifications utilized. The Pathology Department of Memorial Hospital utilizes the following classification for lymphosarcoma: (1) giant follicular lymphosarcoma; (2) reticulum cell sarcoma (RCS); and (3) lymphosarcoma.

By this classification and others, lymphosarcoma occurs most frequently, with RCS next in frequency.[7] It is estimated that 3.5 to 6.3% of childhood cancers are lymphomas; RCS is the pathological diagnosis in 0.8 to 3.19% of the reported series. It is most frequent in boys, with a sex ratio of 3.5 to 1; no race predilection has been described. The association of RCS of bone to RCS of the lymphoid group has not been defined pathologically, but both are known to convert to leukemia, as well as to metastasize and disseminate. If a close relationship is established, this will not markedly increase the

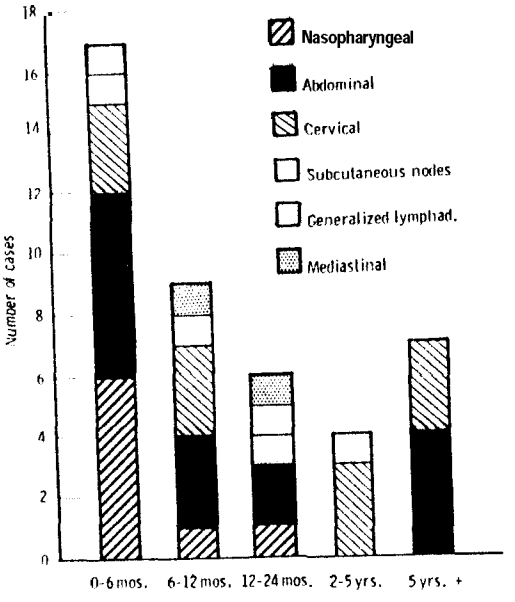

FIG. 3. Clinical forms of onset and survival.

incidence in that reticulum cell sarcoma of bone is also rare.

The beginning symptoms are usually localized, and the form of onset appears to be related to survival. Patients presenting with cervical lymphadenopathy or an abdominal mass have a better prognosis than those seen with a nasopharyngeal mass, generalized lymphadenopathy, or mediastinal involvement (Fig. 3). Previous studies have shown that this is true for the entire group of lymphosarcomas: Bailey et al.,[1] Munson and Marx,[6] arid Charache[2] all reportctl cares of lymphosarcoma of the cervical and abdominal type in which the paticnts survived 5 years or longer.

Zuelzer and Flatz[10] discussed the problem of surgical lesions as a complication of acute leukemia and management of the emergency situation. In RCS, a surgical emergency may lead to the pathological diagnosis, often previously unsuspected. This is illustrated in the following case, which emphasizes that the necessary surgical procedure ran be tolerated and often provides specific pathological diagnosis. As discussed earlier, surgical excision is still the best therapy.

Case 15. J.C., a 5½-year-old white boy, was referred to Memorial Hospital with a chief complaint of vomiting and abdominal pain of 2 months' duration. Barium enema revealed an intussusception. At operation, a mass in the terminal ileum was intussuscepting into the colon, and a right hemicolectomy was performed. The pathological diagnosis was RCS, diffusely infiltrating the bowel. Peripheral blood and bone marrow were within normal limits. No other physical abnormalities were noted. After operation the patient received actinomycin D orally; 6 weeks later this was discontinued when he developed partial obstruction clue to fibrous bands that was relieved by a second surgical procedure. Hepatomegaly and cervical adenopathy were noted at this time. After dircharge he received 6-mercaptopurine orally (2.5 mg. per kg. per day) in a cyclic pattern (3 weeks on and off). Two tnonths later liver and lymph nodes were not palpable.

Three and a half years postdiagnosis and while still on therapy, the patient developed swelling of the upper jaw anti submaxillary lymph nodes and was treatrd by his dentist for dental caries. Because of lack of improvement he was examined under anesthesia, and 3-cm., grayish, soft mass was found occluding the posterior nasopharynx. Biopsy revealed RCS. He received a 1,500-r tumor dose over the nasophatyngeal and submandibulat areas with total regression of the tumor mass. The patient remains well; he was seen last in September 1962, 5 years and 9 months after the onset of the disease.

The incidence of leukemic conversion in RCS in this series is more frequent than has been reported.[8] This probably can be attributed to the more frequent use of bone marrow examination (Table 4). From 1933 to 1953 none of the patients showed leukemic conversion; in the last 9 years, however, of 35 patients admitted to Memorial Hospital with a diagnosis of RCS, 14 developed leukemia (40%). Bone marrow studies were not clone in 5 of the 35. The reported incidence of leukemic conversion in lymphosarcoma ranged from 15%[1,8] to 37%.[3] In children with lymphosarcoma who develop leukemia, the duration of illness is similar to that of patients with acute leukemia (median 44 weeks, average 5 weeks).[9] This has not been the pattern of survival in the group of children reportctl here. All with leukemic conversion showed bone marrow changes within the first 12 months.

TABLE 4

BONE MARROW STUDIES

Period	No. pt	Bone marrow studies, no. pt	
		None	+
1933–1953	10	6	0
1953–1962	35	5	14

kemia developed and the mean was 2.2 months. The mean survival from the beginning of RCS in this group was 8.6 months (Fig. 4).

Despite the generally grave prognosis, 7 of the children have survived more than 5 years. Common characteristics in these patients are as follows:

1. Except in 1 instance, treatment was started within 2 months of diagnosis.
2. All presented with either cervical adenopathy or an abdominal mass.
3. None had leukemic conversion.
4. A radical surgical procedure was done in all but one. Radiotherapy and/or chemotherapy were used in addition.

It is interesting to note that 1 patient with generalized disease and 1 with regional disease have survived 5 years or longer. The result of more intensive therapy in the cases occurring from 1957–1962 cannot yet be evaluated.

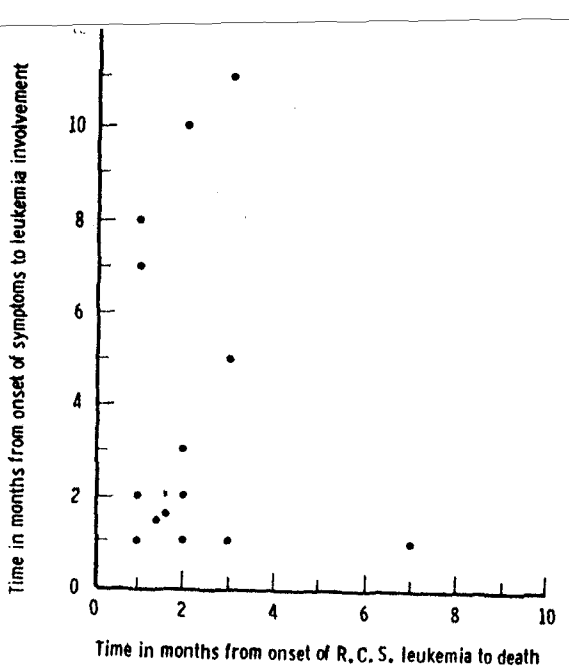

FIG. 4. Time from diagnosis of reticulum cell sarcoma until development of leukemia and survival after conversion. The mean time from onset of symptoms to leukemia involvement was 3.9 months. The mean survival time after the conversion to leukemia was 2.2 months.

SUMMARY

The clinical picture, management, and prognosis of 45 children with reticulum cell sarcoma (RCS) has been presented. The prognosis of RCS in children is better if the form of onset is abdominal or cervical, and if leukemic conversion does not develop within the first 2 months. The incidence of leukemic conversion rises to at least 40% when this possibility is investigated. In these cases, the response to the usual treatment is poor, and the median duration of life is shorter than in children with acute stem cell leukemia. Alteration of prognosis (mean survival or 5-year cures) may be provided by early diagnosis, surgical resection when feasible, and the addition of radiotherapy and/or chemotherapy. More controlled studies are necessary.

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