Hydantoin-Induced Pseudo-Pseudolymphoma

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SUMMARY **A patient developed lymphadenopathy while receiving diphenylhydantoin therapy that histologically resembled malignant lymphoma. Adenopathy regressed when diphenylhydantoin was discontinued but subsequently recurred as a fatal, malignant lymphoma.**

Previous reports of hydantoin-induced lymphadenopathy were reviewed and classified. It was found that no consistent clinical or histologic criteria existed to differentiate benign from malignant lymphoid reactions.

IN 1959 SALTZSTEIN and Ackerman (1) reported that hydantoin drugs may cause lymphadenopathy that mimics malignant lymphomas. Most patients with hydantoin-induced lymphadenopathy experience prompt improvement with regression of all nodal enlargement after cessation of the offending drug (1, 4–16). However, 3 to 5 years after this Saltzstein and Ackerman report, two of their seven patients developed and died of lymphoma (2). Recently, Hyman and Sommers (3) reported seven patients who developed malignant lymphomas in association with anticonvulsant therapy. The authors believed they could clearly differentiate these cases of true lymphoma from benign, drug-induced lymphadenopathy on histologic and clinical grounds.

We have had the opportunity to follow a patient who developed lymphadenopathy while on diphenylhydantoin therapy. His disease was histologically indistinguishable from malignant lymphoma. Despite prompt regression of lymphadenopathy with cessation of the hydantoin, a fatal lymphoma subsequently developed. The sequence of events in this case prompted a review of the pathologic aspects of hydantoin-associated lymphadenopathy and a reconsideration of the possible interrelationships of the various manifestations of this syndrome.

CASE REPORT

J. C., a 45-year-old negro man, was well until December 1961 when he had a grand mal seizure while asleep. Neurological evaluation was within normal limits, and he was placed on diphenylhydantoin, 200 mg at night, and phenobarbital, 64 mg every 6 hr. He did well, and medication was discontinued after 6 months. Twelve days later he had another grand mal seizure, and diphenylhydantoin, 100 mg three times a day, and phenobarbital, 64 mg every 6 hr, was reinstituted.

Six months later (December 1962) he noticed swelling of the right side of his neck. A physician discovered several enlarged lymph nodes. Biopsy was interpreted as chronic reactive lymphadenitis (Figure 1). Five months later, in April 1963, a suprasternal mass was excised that was interpreted as a malignant lymphoma, pleomorphic malignant histiocytic type (Figure 2). The pertinent feature of this biopsy was its frankly malignant character in contrast to the original biopsy.

Physical examination demonstrated bilateral, posterior, cervical lymph node enlargement. Several small lymph nodes were present in both axillae and inguinal regions. The liver was of normal size, and the spleen was not palpable. Chest X ray was within normal limits.

The possibility was entertained that the malignant lymph node changes were induced by diphenylhydantoin, and so the medication was discontinued in the hopes that the lymph node enlargement would regress. Two months later all lymph node enlargement had receded.

In December 1963 and again in April 1964, 8 and 12 months after hydantoin withdrawal, physical examinations were entirely within normal limits. During the late summer and fall of 1964, he started to feel poorly and was readmitted to the hospital in December 1964, 20 months after hydantoin withdrawal, with a 6-month history of nausea, eructation, upper abdominal pain, and a 20-lb weight loss. Physical examination demonstrated large, firm lymph nodes in the right preauricular and bilateral cervical areas. A firm, fixed 3×14-cm mass was palpated in the infraumbilical area. The liver, kid-

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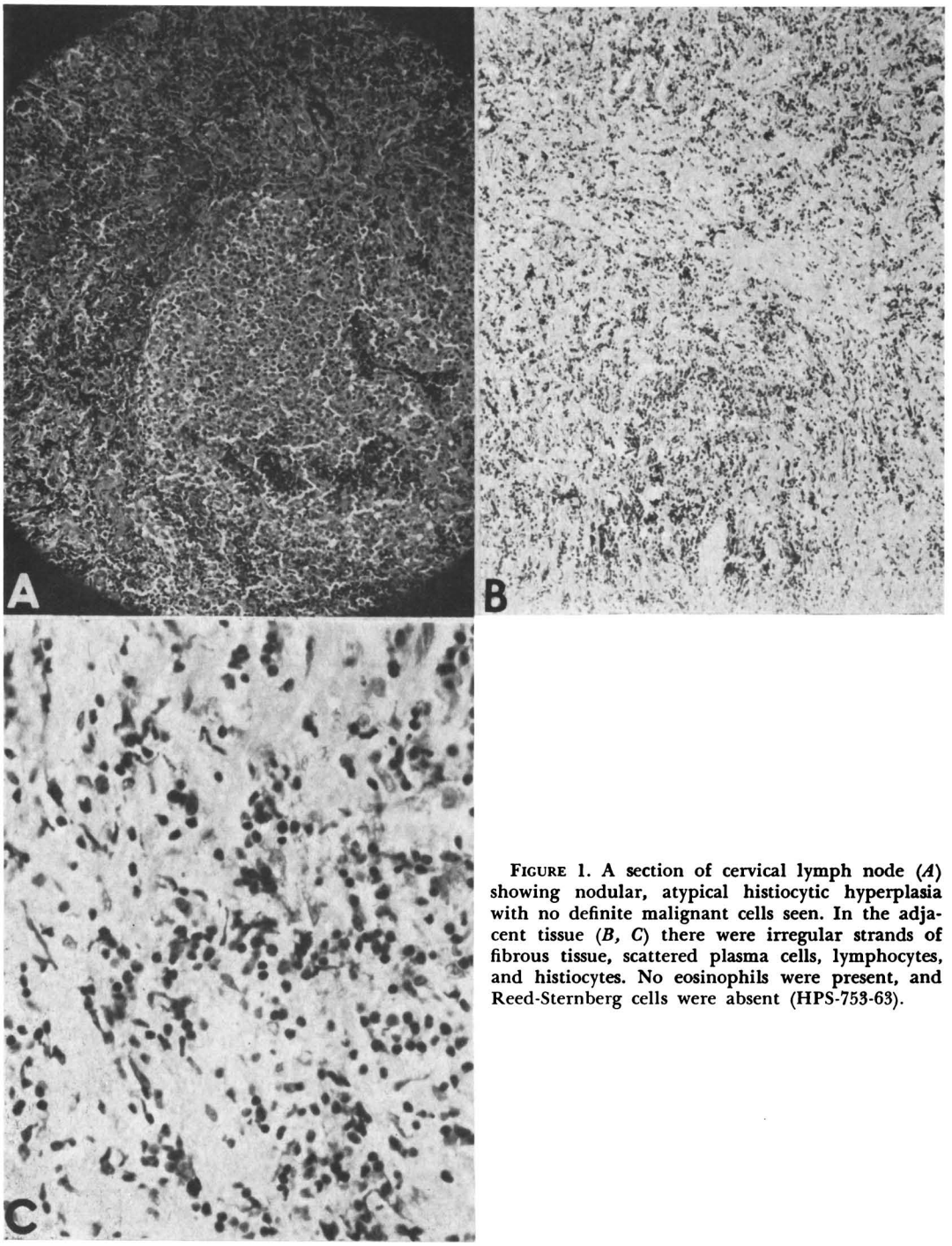

FIGURE 1. A section of cervical lymph node (*A*) showing nodular, atypical histiocytic hyperplasia with no definite malignant cells seen. In the adjacent tissue (*B, C*) there were irregular strands of fibrous tissue, scattered plasma cells, lymphocytes, and histiocytes. No eosinophils were present, and Reed-Sternberg cells were absent (HPS-753-63).

neys, and spleen were not palpable. The remainder of the physical examination was within normal limits. An upper gastrointestinal series and esophagogastroscopy were suggestive of an infiltrative process of the gastric fundus. A lymphangiogram of the retroperitoneal lymph nodes was grossly abnormal. A biopsy of an anterior cervical lymph node was interpreted as malignant lymphoma, poorly differentiated histiocytic type (Figure 3).

Nitrogen mustard therapy was administered in a dose of 0.4 mg/kg followed by maintenance oral cyclophosphamide in a dose of 50 mg/day. The

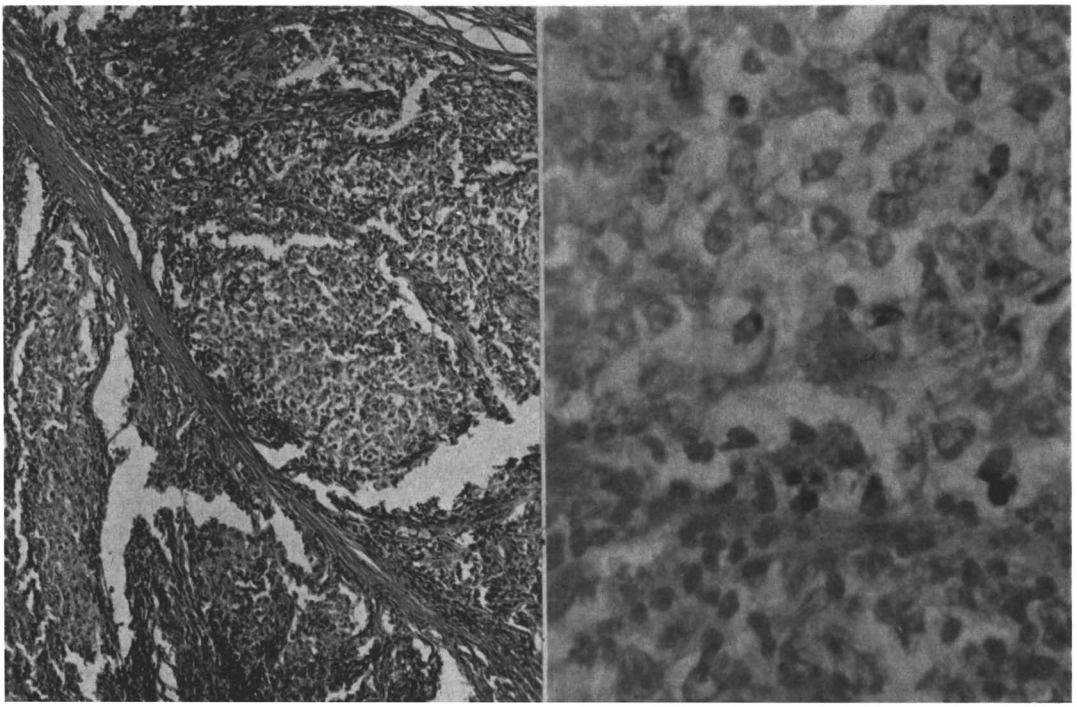

FIGURE 2. Biopsy of suprasternal mass showing residual strands of lymphoid tissue compressed by proliferating masses of malignant histiocytes that showed nuclear pleomorphism. Many of these bizarre nuclei possessed enlarged nucleoli and had mitotic figures (HPS-5016-63).

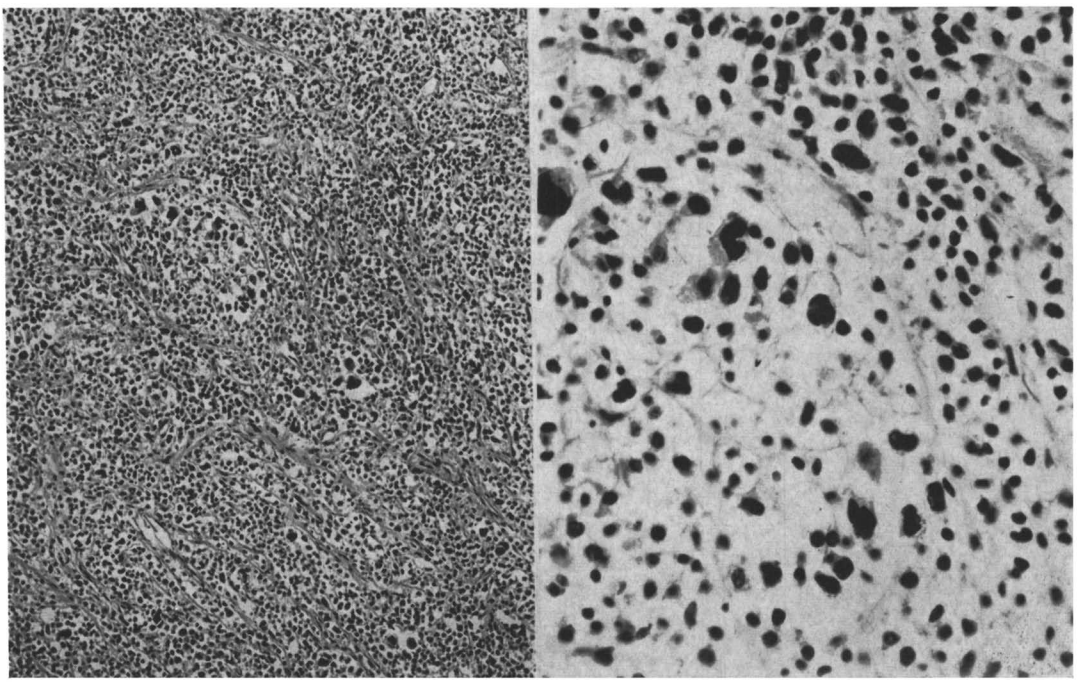

FIGURE 3. Biopsy of an anterior cervical lymph node showing complete obliteration of normal lymph node architecture by young malignant histiocytes. There were marked pleomorphism of individual nuclei, clumping of chromatin, and prominent nucleoli. No Reed-Sternberg cells were present (HPS-1142-64).

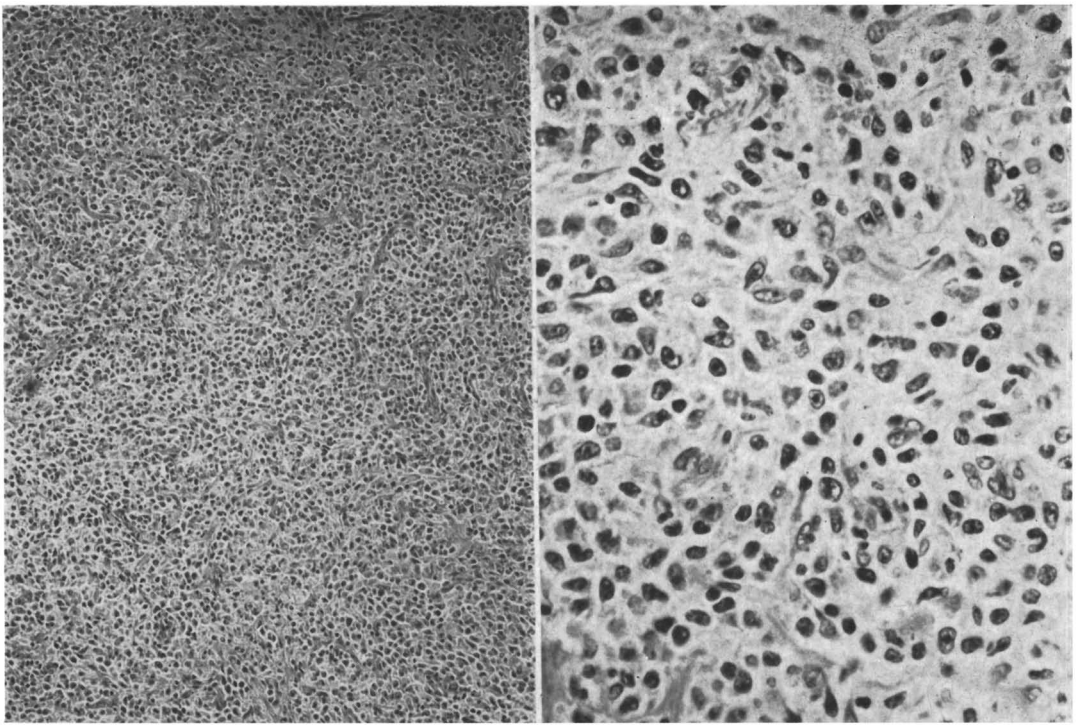

FIGURE 4. Autopsy specimen showing numerous bizarre, giant histiocytes and reticulum cells scattered throughout the lymph nodes. These cells contain hyperchromatic and lobulated nuclei with large, prominent inclusion-body-type nucleoli (HPA-205-65).

patient was discharged from the hospital, but his disease progressed unabated. His final admission was in June 1965 at which time he died from generalized lymphoma. At necropsy it was found that lymphomatous involvement had caused obstruction and perforation of the proximal jejunum. The right kidney, duodenum, stomach, and mesentery were all involved with nodular masses. The second and third lumbar vertebrae contained a tumor, and the right ureter was partially obstructed. The histologic appearance of the lymphoma at autopsy showed a malignant lymphoma of pleomorphic histiocytic type (Figure 4).

DISCUSSION

Lymphadenopathy may be seen in association with the use of a variety of drugs (17) including hydantoin, para-aminosalicylic acid, iron dextran, phenylbutazone, and meprobamate. However, since the report of Saltzstein and Ackerman (1), hydantoin-induced lymphadenopathy has received the greatest attention. Although originally regarded as a benign complication of hydantoin therapy, it is now clear that the use of these anticonvulsants can be associated with the development of a malignant lymphoma (3).

Hyman and Sommers (3) have used the term "pseudolymphoma" to describe a syndrome of lymphadenopathy, fever, and a morbilliform rash, with the frequent association of joint pain and swelling, hepatomegaly, splenomegaly, and eosinophilia. The lymphadenopathy promptly recedes with cessation of drug therapy but recurs if the drug is reintroduced. Lymph node biopsy may resemble lymphoma grossly, but histologically it lacks obliteration of architecture, invasion of node capsule or blood vessel walls, and malignant neoplastic cells are not seen. This syndrome is a benign condition in contrast to "true" malignant lymphoma that Hyman and Sommers felt is clearly recognizable microscopically and that lacks the associated clinical findings noted above.

The present case showed histologic features of hyperplasia and then frank malignant lymphoma, yet the generalized lymphadenopathy promptly regressed when diphenylhydantoin was discontinued only to recur 1½ years later as a fatal malignant lymphoma. Since features

TABLE 1A. Hyperplasia: Architecture Preserved, Pleomorphic Response, Clearly Benign

Case	Reference Number	Age, Sex	Drug	Nodes	Rash	Fever	Eosinophils	Hepatosplenomegaly*	Pathology	Regression After Cessation of Therapy	Follow-Up
1.	6	29 M	Dilantin®	Cervical, axillary, inguinal	+	+	+	H	"Chronic inflamation. Pleomorphic cellular response	Yes	No follow-up available.
2.	1 (Case 2)	6 M	Mesantoin®, dilantin	Cervical, axillary, inguinal	+	+	+	O	Pleomorphic hyperplasia; lymphocyte and reticulum. Eosinophilia. Foci of necrosis.	Yes	No recurrence after 4 years.
3.	1 (Case 5)	10 M	Mesantoin, dilantin	Cervical	+	+	+	H	Pleomorphic hyperplasia; lymphocyte and reticulum. Slight fibrosis.	Yes	No recurrence after 2 years.
4.	10	6 F	Dilantin	Generalized	+	+	+	H-S	Pleomorphic hyperplasia; lymphocyte and reticulum. "Chronic lymphadenitis."	Yes	No recurrence after 1½ months.
5.	15	14 M	Mesantoin	Axillary, inguinal	+	+	+	S	Reticulum cell hyperplasia. "Chronic lymphadenitis."	Yes	No follow-up available.
6.	8	46 M	Mesantoin	Cervical	+	+	0	H	Pleomorphic hyperplasia; lymphocyte and reticulum.	Died of dehydration before cessation of drug could be evaluated.	
7.	11	18 F	Mesantoin	Generalized	+	+	+	O	Pleomorphic hyperplasia. Eosinophilia. "Nonspecific lymphadenitis."	Yes, after steroid therapy	Positive lupus erythematosis preparation. Diagnosis: systemic lupus erythematosus. No follow-up available.

* H = hepatomegaly; S = splenomegaly; O = neither.

of both "pseudolymphoma" and "true lymphoma" as described by Hyman and Sommers (3) were present in this case, the clinical and pathologic features of previously reported cases of hydantoin-induced adenopathy in which microscopic descriptions were present were reviewed (1–16) in order to assess the reliability of the clinical picture, histopathology, and regression of lymphadenopathy in determining the benign or malignant nature of the condition. Tables 1 and 2 summarize the findings from these cases.

It was found that hydantoin-induced lymphadenopathy may be separated into four major categories—hyperplasia, pseudolymphoma, pseudo-pseudolymphoma, and lymphoma (Table 1). The hyperplasia group (Table 1A) demonstrated normal lymph node architecture with a pleomorphic cellular response or lymphadenitis in some instances. Lymphadenopathy regularly regressed with cessation of therapy. This group is not confused with lymphoma on biopsy and corresponds to the group Hyman and Sommers (3) labeled pseudolymphoma. We feel the term pseudolymphoma is more appropriately applied to the second group (Table 1B), which was clinically indistinguishable from the hyperplasia group but demonstrated alteration and effacement of nodal architecture with reticulum cell hyperplasia, often to the point of appearing frankly malignant. Again, prompt regression and lack of recurrence of adenopathy regularly followed cessation of hydantoin therapy. Those patients reported by Hyman and Sommers (3) with frankly malignant histologic changes and lack of regression of adenopathy constitute the lymphoma group (Table 1D).

Between the pseudolymphoma and lymphoma groups are the patients described in this report and those reported in 1958 and in 1962 (1, 2). These patients (Table 1C) showed hyperplasia or malignant changes in biopsied lymph nodes, but the adenopathy regressed when hydantoin was stopped. After an asymptomatic quiescent period, there was development of malignant lymphoma and subsequent death. We have labeled this sequence of events pseudo-pseudolymphoma.

Saltzstein (2) has stated that a pleomorphic cellular response is indicative of hydantoin lymphadenopathy. This holds true for the easily recognized benign hyperplasia group. In the more difficult pseudolymphoma group, however, it appears that a reticulum cell or histiocytic response is more prevalent, with an occasional cell resembling the Reed-Sternberg cell described. Fibrosis, eosinophilia, and necrosis may also be present in this group but only in small foci and not predominating the histologic picture. The patients with pseudo-pseudolymphoma, although clinically somewhat different, had biopsies very similar to the pseudolymphoma group. There were a reticulum cell hyperplasia and bizarre reticulum cells. The histologic differentiation of these two groups is very difficult. The frankly malignant group of patients reported by Hyman and Sommers (3) presented little difficulty in pathologic diagnosis. Except for Case 5, in which there was some difference of opinion, all patients had obviously malignant disease with easily recognized characteristics of Hodgkin's disease, reticulum cell sarcoma, or lymphosarcoma.

Table 2 demonstrates that there was little difference in the first two groups with respect to associated rash, fever, eosinophilia, or hepatosplenomegaly, but that there was a definite clinical difference between these and the last two groups. The microscopic anatomy in the pseudolymphoma group could not be readily distinguished from true lymphoma. The clinical course demonstrated by the three patients in the "pseudo-pseudolymphoma" group points up the unreliability of depending on the regression of adenopathy with cessation of hydantoin as a test of benignity.

A comparison of the ages of the four groups shows the members of the hyperplasia group to be much younger than those in the other groups (Table 2) but shows no real difference among the latter three groups. There does not appear to be a sex difference among the four groups.

Lymphadenopathy associated with hydantoin thus represents a spectrum of lymphoid reaction, both histologically and clinically. Lymphoid hyperplasia or microscopic "pseudolymphoma" may regress with cessation of hydantoin never to recur unless therapy is reinstituted. Frank lymphoma may occur that does not regress after therapy is stopped. In three patients to date, regression of lymphadenopathy was followed by recurrence of fatal malignant lymphoma several years later.

TABLE 1B. Pseudolymphoma: Reticulum Cell Hyperplasia, Suspicious for Malignant Lymphoma

Case	Reference Number	Age, Sex	Drug	Nodes	Rash	Fever	Eosinophils	Hepatosplenomegaly*	Pathology	Regression After Cessation of Therapy	Follow-Up
1.	5	Not given	Mesantoin®	Not specified	+	+	0	O	"Indistinguishable from Hodgkins."	Yes	No follow-up available.
2.	13	30 F	Mesantoin	Supraclavicular	+	+	+	H	Reticulum cell hyperplasia with numerous mitoses, capsular and subcapsular sinusoidal invasion. Increased eosinophils and plasma cells. "Reed-Sternberg" cells.	Yes	No recurrence after 3 years.
3.	1 (Case 1)	11 M	Milontin®	Mesenteric	0	0	0	O	Reticulum cell hyperplasia. Increased mitoses. Eosinophilia. Foci of necrosis. "Malignant lymphoma."	Yes	No recurrence after 5 years.
4.	12	31 F	Dilantin®	Axillary, cervical	+	+	+	H-S	Lymphatic hyperplasia with mitoses. Increased fibrosis. "Lymphoblastic lymphosarcoma."	Yes	No follow-up available.
5.	16	36 M	Mesantoin	Axillary, cervical	+	+	+	S	Reticulum cell hyperplasia. Increased eosinophils and plasma cells. Focal necrosis. "Reed-Sternberg" cells; "Hodgkin's disease."	Yes	No recurrence after 7 years.
6.	7 (Case 1)	21 M	Mesantoin	Cervical	+	0	+	O	Reticulum cell hyperplasia. Eosinophilia. Foci of necrosis.	Yes	No follow-up available.
7.	7 (Case 2)	47 M	Mesantoin	Generalized	+	+	0	O	Reticulum cell hyperplasia. Mitoses. Eosinophilia. Foci of necrosis.	Yes	No follow-up available.
8.	9	5 M	Dilantin	Generalized	+	+	0	O	Reticulum cell hyperplasia. Diffuse sclerosis.	Yes	No follow-up available.

* H = hepatomegaly; S = splenomegaly; O = neither.

TABLE 1B. Pseudolymphoma: Reticulum Cell Hyperplasia, Suspicious for Malignant Lymphoma (*Continued*)

Case	Reference Number	Age, Sex	Drug	Nodes	Rash	Fever	Eosinophils	Hepatosplenomegaly*	Pathology	Regression After Cessation of Therapy	Follow-Up
9.	1 (Case 6)	7 M	Peganone®	Axillary, cervical	0	+	+	H-S	Pleomorphic hyperplasia. Reticulum, lymphocyte, plasma cell, eosinophilia. Foci of necrosis. Capsular invasion.	Yes	No recurrence after 4 months.
10.	14	71 M	Primidone®	Cervical	+	+	+	O	Reticulum cell hyperplasia. Eosinophilia. Foci of necrosis (October 1965).	Yes	Died of cancer of stomach, July 1967. No lymphoma.
11.	8	56 M	Mesantoin	Cervical	+	+	+	O	Reticulum cell hyperplasia. Eosinophilia. Foci of necrosis.	Yes	No follow-up available.
12.	8 (Case 2)	31 F	Mesantoin	Cervical, inguinal	+	0	0	O	Reticulum cell hyperplasia. Eosinophilia. Foci of necrosis.	Yes	No follow-up available.
13.	1 (Case 7)	45 F	Dilantin	Generalized	+	+	+	O	Reticulum cell hyperplasia. Increased plasma cells. Eosinophilia.	Yes	No recurrence after 2 months.
14.	4	71 M	Dilantin	Cervical	+	0	0	O	Reticulum cell hyperplasia. Eosinophilia.	Died of periarteritis	Diagnosis: reactive lymphadenitis secondary to exfoliative dermatitis.

TABLE 1C. Pseudo-Pseudolymphoma: Reticulum Cell Hyperplasia, Suspicious or Frankly Malignant

Case	Reference Number	Age, Sex	Drug	Nodes	Rash	Fever	Eosinophils	Hepatosplenomegaly*	Pathology	Regression After Cessation of Therapy	Follow-Up
1.	1 (Case 4, 2)	26 M	Dilantin® Mesantoin® Mysoline®	Generalized	+	+	+	H-S	September 1956. Reticulum cell hyperplasia. Mitoses. Eosinophilia.	Yes, twice	
									January 1960. Pleomorphic hyperplasia. Eosinophilia.	No	
									May 1960. Reticulum cell hyperplasia. "Malignant lymphoma."		Died of lymphoma.
2.	1 (Case 3)	53 F	Dilantin	Cervical, axillary, inguinal	0	0	0	O	Reticulum cell hyperplasia. Eosinophilia. Increased plasma cells. Foci of necrosis.	Yes, twice	Died of multiple myeloma.
3.	Present case	45 M	Dilantin	Generalized	0	0	0	O	December 1962. Reticulum cell hyperplasia. Slight fibrosis.		
									April 1963. Reticulum cell hyperplasia. Increased mitoses.	Yes	
									December 1964. Reticulum cell hyperplasia. "Malignant lymphoma."		Died of diffuse lymphoma.

* H = hepatomegaly; S = splenomegaly; O = neither.

TABLE 1D. Lymphoma

Case	Reference Number	Age, Sex	Drug	Nodes	Rash	Fever	Eosinophils	Hepatosplenomegaly*	Pathology	Regression After Cessation of Therapy
1.	3 (Case 1)	27 F	Dilantin® Mysoline® Celontin®	None	0	0	0	O	Anaplastic multinucleated reticulum cells. Reed-Sternberg cells. Hyaline nodules. "Nodular sclerosing Hodgkin's disease."	No, Dilantin not stopped.
2.	3 (Case 2)	22 F	Dilantin	Cervical	0	+	0	O	Lymphocyte hyperplasia. Reed-Sternberg cells. "Lymphocyte predominant Hodgkin's disease."	No, Dilantin not stopped.
3.	3 (Case 3)	23 F	Dilantin	Cervical, axillary	0	0	0	S	Lymphocyte hyperplasia. Reed-Sternberg cells. Capsular invasion. Eosinophilia. Foci of necrosis. "Lymphocyte predominant Hodgkin's disease."	No
4.	3 (Case 4)	62 M	Dilantin	Generalized	0	0	0	S	Lymphocyte hyperlpasia. Capsular invasions. "Lymphosarcoma."	No, Dilantin not stopped.
5.	3 (Case 5)	68 M	Dilantin	None	0	+	0	O	January 1957. Lymphocyte hyperplasia. Pleomorphic. "Consistant with atypical hyperplasia secondary to hydantoins." July 1959. Lymphocyte hyperplasia. Capsular invasion. "Lymphoblastic lymphosarcoma."	No, Dilantin not stopped.
6.	3 (Case 6)	65 M	Dilantin	Abdominal	0	0	0	O	No description. "Reticulum cell sarcoma."	No, Dilantin not stopped.
7.	3 (Case 7)	30 M	Dilantin	Cervical, axillary	0	0	0	O	Reticulum cell hyperplasia. Reed-Sternberg cells. "Hodgkin's disease."	No, Dilantin not stopped.

* H = hepatomegaly; S = splenomegaly; O = neither.

TABLE 2. Comparison of Four Age Groups

Type	Number of Patients	Age Range	Average Age	Sex M/F	Rash	Fever	Eosinophils	Hepatosplenomegaly	Predominant Cell Type	Regression After Cessation of Therapy
Hyperplasia	7	6–46	18	5/2	7	7	6	4–2	Pleomorphic, 6; reticulum, 1.	6
Pseudo-lymphoma	14	5–71	36	9/4	12	10	8	4–3	Reticulum cell, 12; pleomorphic, 1; lymphocytic, 1.	13
Pseudo-pseudo-lymphoma	3	26–53	41	2/1	1	1	1	1–1	Reticulum cell, 3.	3
Lymphoma	7	22–68	42	4/3	0	2	0	0–2	Lymphocyte, 4; reticulum, 3.	0

The question that remains unanswered is whether or not hydantoin may induce malignant changes in lymphoid tissues, or whether these cases represent the fortuitous association of treatment and lymphoma unrelated as to cause and effect. Limited experimental evidence (18) indicates that hydantoins are lymphostimulatory, but there is no evidence that they are able to cause malignant change directly. It is very possible that through their lymphostimulatory action, hydantoins may unmask underlying lymphomas. So far, despite the fact that all hydantoins may induce lymphadenopathy, only diphenylhydantoin has been associated with a malignant lymphoma.

Regardless of the exact role of hydantoins in the cause of lymphoma, it is clear that all associated hydantoin adenopathy is not universally benign. Although maintenance of normal lymph node architecture and prompt regression of adenopathy with cessation of hydantoin favor a benign prognosis, all such patients must be observed closely for the early recognition of a recurring malignant lymphoma.

In view of the lack of long-term follow-up information on the majority of previously reported cases (Tables 1A and 1B), the eventual development of a malignant lymphoma—despite regression of adenopathy when hydantoin is discontinued—may some day prove to be the rule rather than the exception in patients with hydantoin-induced lymphadenopathy.

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