Reprinted from the Archives of Internal Medicine
October 1979, Volume 139

Solid Tumors Complicating Hodgkin's Disease

A Report on Two Patients With Immunoglobulin Deficiency

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• **Multiple epithelial malignant neoplasms developed in two patients with Hodgkin's disease subsequent to radiotherapy and intensive chemotherapy. At the time of diagnosis, each patient also demonstrated a serum immunoglobulin deficiency. The significance of the occurrence of solid tumors in patients following therapy for Hodgkin's disease and the significance of cellular and humoral immunodeficiency in Hodgkin's disease in relation to second cancer development were studied. We suggest the establishment of a registry of leukemias and solid tumors developing in patients treated for Hodgkin's disease and other malignant neoplasms, possibly with detailed recording of immunocompetence data.**

(*Arch Intern Med* 139:1131-1134, 1979)

A higher incidence of second cancers in Hodgkin's disease has been observed by several authors.[1-9] Most of the subsequent malignant neoplasms reported have been acute myelocytic leukemias.[1,5,6,9,10] The probability of the development of leukemia in treated patients with Hodgkin's disease is expected to be 2.0% at seven years.[6] The risk is greatest in patients treated with both irradiation and multiple agent chemotherapy.[1,5,6] It is believed that the higher incidence of leukemia might be the result of intensive combined therapy, improved survival, and possibly other unknown factors.

In contrast to acute leukemia, the occurrence of nonhematological malignant neoplasms in patients with Hodgkin's disease has received little attention. The incidence of solid tumors in various reports has varied from 0.5% to 6.6%.[1-4,7,8,10,11] The tendency has been to consider the risk of development of solid tumors in Hodgkin's disease not to be increased over that expected in the general population.[1,3,7]

The immunosuppressive potential of therapeutic modalities used in treating Hodgkin's disease is well recognized.[12,13] It is also known that there is an increased risk of developing malignant neoplasms in a variety of disorders characterized by a primary or secondary deficit in cellular and humoral immune mechanisms.[14,15] The oncogenic potential of multimodality therapy might in part operate through a permanent deleterious effect on the immune system of the host.

This report describes two patients with treated Hodgkin's disease who were in prolonged complete remission when solid tumors developed. It is interesting that, at the time of diagnosis of the second primary tumor, serum immunoglobulin deficiencies were noted in both patients.

REPORT OF CASES

Case 1.—In May 1968 (Table 1), left posterior cervical adenopathy developed in a 29-year-old man. Hodgkin's disease, mixed cellularity, was diagnosed on node biopsy and was treated by irradiation (4,150 rads of tumor dose to the left side of the neck, 2,400 rads of tumor dose to the right side of the neck, and 3,800 rads of tumor dose to the mediastinal nodes). This resulted in complete remission. In December 1972, he was readmitted because of recurrent disease manifested by hepatosplenomegaly. He was treated with mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) from December 1972 to December 1973; a complete remission was obtained.

Between 1972 and 1976, he had numerous upper respiratory tract infections for which he received antibiotic treatments. In January 1976, serum immunoglobulin levels were IgA, 0 mg/dL (normal, 156 to 294 mg/dL); IgM, 98 mg/dL (normal, 67 to 145 mg/dL); IgG, 1,950 mg/dL (normal, 1,000 to 1,800 mg/dL). Repeat study six months later showed the following values: IgA, 2.3 mg/dL; IgM, 90 mg/dL; IgG, 2,050 mg/dL.

In January 1977 he was hospitalized because of weakness, weight loss, fever, jaundice, and hepatomegaly. A liver scan done on Jan 15, 1977, disclosed areas of decreased uptake. The α-fetoprotein determination yielded negative results, but the carcinoembryogenic antigen level was 72 ng/mL. A needle biopsy of the liver showed pleomorphic elements with a few cells highly suggestive of Reed-Sternberg cells. The patient was restarted on MOPP therapy on Feb 4, 1977, and he received three cycles. His symptoms improved; however, in April, while still on MOPP therapy, he was readmitted with pleuritic chest pain, productive cough, and moderate dyspnea. Roentgenograms of the chest disclosed bilateral parenchymal infiltrates. A search for viral, bacterial, and fungal organisms was unrewarding. Before successful conclusion of the investigations, the patient left the hospital

Accepted for publication March 19, 1979.

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Table 1.—Immune Values at Time of Diagnosis of Second Neoplasm

	Immune Status						
	B Cell				T Cell		
Date	IgG, mg/dL	IgA, mg/dL	IgM, mg/dL	Other	Peripheral Lymphocytes/cu mm	Skin Tests	Other
				Case 1*			
6/76	1,950	0	98.0	. . .	. . .	All negative†	. . .
9/76	2,050	2.3	90.0	. . .	72-2,024	. . .	. . .
1/77	1,774	0	93.9	. . .	. . .	. . .	. . .
				Case 2‡			
4/78	826	137.8	45.2	Secretory IgA (saliva), 0; rosette (EAC) = 21% (normal = 20%-25%)	3,822	PPD and *Monilia* positive, others negative	Rosette (E) = 41% (normal = 55%-65%)

*Case 1: Interval between diagnosis of Hodgkin's disease and second malignant neoplasm (poorly differentiated large cell carcinoma of lung with disseminated metastasis, adenocarcinoma of right kidney) was nine years. Treatment for Hodgkin's disease comprised radiotherapy and MOPP. Length of complete remission of Hodgkin's disease was four years.

†Skin tests: PPD, mumps, *Monilia, Trichophyton,* dinitrochlorobenzene (DNCB).

‡Case 2: Interval between diagnosis of Hodgkin's disease and second malignant neoplasm (well-differentiated squamous cell carcinoma of cervix, vaginal wall, and perineum) was 13 years. Treatment for Hodgkin's disease comprised radiotherapy, prednisone and chlorambucil, MOPP, and BCG vaccine. Length of complete remission of Hodgkin's disease was 3½ years.

against medical recommendation.

The final admission in May 1977 was precipitated by worsening dyspnea. On examination, there was hepatomegaly but no enlarged lymph nodes. A chest roentgenogram showed more extensive pulmonary infiltrates with questionable cavitation. The hemoglobin level was 8.5 mg/dL; hematocrit reading, 27.8%; WBC count, 12,700/cu mm; polymorphonuclear leukocytes, 82%; band forms, 9%; lymphocytes, 9%; and monocytes, 11%. The platelets were 154,000/cu mm. A liver profile showed a bilirubin value of 1.5 mg/dL; direct bilirubin value, 1.9 mg/dL; SGOT content, 65 mU/mL; SGPT content, 27 mU/mL; alkaline phosphatase level, 1,350 IU/L. The γ-glutamyl-transpeptidase level was 584 IU/L (normal 24 to 48 IU/L). Numerous serological and microbiological studies were unrewarding. Cytological examination of the sputum disclosed malignant cells with epidermoid features. However, before specific therapy could be instituted, the patient died.

Autopsy demonstrated the following: (1) poorly differentiated large cell carcinoma of the left upper lobe of the lung with foci of extension to the ipsilateral lower lobes and lymphangitic spread, fibrosis, large areas of necrosis with cavitation, and vascular and lymphatic invasion by the neoplasm; (2) metastatic spread to the opposite lung and all groups of lymph nodes above and below the diaphragm, to the adrenal glands, liver, and bones; (3) no evidence of Hodgkin's disease; (4) adenocarcinoma in situ (tubular adenoma) of the right kidney present in one random section.

CASE 2.—A 30-year-old woman had a right submandibular swelling in April 1965 (Table 1). A diagnosis of Hodgkin's disease of mixed cellularity type was made on biopsy of the submandibular node. From December 1965 to January 1966, she received 2,800 rads of tumor dose to the right side of the neck, 1,265 rads to the left side of the neck, and 1,000 rads to the right axilla. She remained symptom free until May 1968, when she had recurrence with fever, weight loss, and anemia. She received blood transfusions and mechlorethamine hydrochloride; her symptoms cleared.

In January 1969, fever again developed. She received another full cycle of mechlorethamine hydrochloride (0.2 mg/kg × 2) and was then given maintenance doses of prednisone, 5 to 15 mg, and chlorambucil, 2 to 6 mg daily, until August 1972. She underwent an exploratory laparotomy and splenectomy on Aug 31, 1972. Liver, lymph node, and bone marrow biopsies at operation failed to show Hodgkin's disease. In October 1972, episodes of fever developed and she was found to have a palpable lymph node, 2.8 × 2.2 cm, in the left supraclavicular area. She was started on combination chemotherapy with MOPP. She had six cycles of MOPP, with several interruptions due to nausea and vomiting, as well as poor patient attendance. In April 1973 at the conclusion of MOPP therapy, she was in complete remission.

Immunotherapy with BCG vaccine was started in November 1973 using 0.1 mL intradermally. In September 1974, after only five doses, this therapy was stopped when adenitis with a draining sinus developed in the left axilla, which was positive on smear for acid-fast bacilli interpreted as BCG. She then received isoniazid, 300 mg daily; the lesion healed within six months and she remained in complete remission.

In February 1978, she was readmitted for excision biopsy of a warty lesion of the perineal region. This biopsy showed well-differentiated squamous cell carcinoma. Further biopsy specimens taken from vaginal wall and cervix uteri in April disclosed well-differentiated squamous cell carcinoma. Immunoglobulin values were as follows: IgG, 826 mg/dL (normal, 1,000 to 1,800 mg/dL); IgA, 137.8 mg/dL (normal, 156 to 294 mg/dL); IgM, 45.2 mg/dL (normal, 67 to 145 mg/dL); the secretory IgA level in saliva was reported as 0 mg/dL. In June 1978, a total abdominal hysterectomy with proximal vaginal cuff was done. The pathological interpretation was that the perineal, cervical, and vaginal lesions were each a separate primary neoplasm of the squamous cell type.

COMMENT

The occurrence of second cancers in patients with Hodgkin's disease has been noted by several authors and is attracting increased attention. The reported incidence of a second malignant neoplasm in patients with Hodgkin's disease varies from 1.6% to 2.2%, which is 14.5 to 24 times that found in the general population.[1,5] The leukemogenic potential of irradiation and anticancer drugs is well recognized, and irradiation and anticancer drugs used for the treatment of Hodgkin's disease have been implicated as possible causal factors.[1-4,9] Canellos et al found the overall incidence of second neoplasms in Hodgkin's disease to be 14.5 times higher than expected. In a subgroup of patients who were in complete remission following extensive irradiation (IR) and intensive combination chemotherapy (IC), the incidence was 18.5 times expected.[5] Arseneau et al also concurred that the patients treated with both IR and IC were at greater risk.[1] Most of the attention has been centered on the development of acute myelocytic leukemia, since irradiation has been recognized as being leukemogenic.[9] Coleman et al, in a group of patients with Hodgkin's disease, calculated the probability of developing acute leukemia at seven years to be 2.0%.[6]

Curiously, reports of solid tumors occurring in patients

Table 2.—Subsequent Solid Tumors in Hodgkin's Disease

Tumor Type	Present Study	Arseneau* et al[1]	Berg[2]	Bonnadonna et al[3]	Brody et al[4]	Moertel and Hagedorn[10]	Neufeld et al[7]	Penn†[8]	Razis et al[11]	Total
Sarcomas	...	2	3	...	5	...	1	3	2	**16**
Skin, epidermoid	...	1	5	...	3	...	...	2	4	**15**
Epidermoid cancers										
Vulva and cervix	1	...	...	...	...	...	...	1	1	**3**
Head and neck	...	...	...	...	2	...	1	...	2	**5**
Bladder	...	...	1	...	1	...	...	6	...	**8**
Lung	...	...	...	...	2	1	...	1	1	**5**
										21
Adenocarcinomas										
Gastrointestinal	...	...	2	...	4	4	...	1	3	**14**
Breast	...	...	1	...	3	1	...	1	2	**8**
Ovary	...	...	...	...	1	...	...	...	1	**2**
Prostate	...	...	...	...	...	1	1	1	1	**4**
Endometrium	...	...	...	...	1	...	...	...	1	**2**
Lung	1	...	...	...	...	...	...	...	...	**1**
										31
Others										
Melanoma	...	...	...	1	1	...	...	...	1	**3**
Brain	...	...	1	...	...	...	...	...	...	**1**
Thyroid	...	...	...	...	...	1	...	...	1	**2**
										6
No. of solid tumors	**2**	**3**	**13**	**1**	**23**	**8**	**3**	**16**	**20**	**89**
No. of cases of Hodgkin's disease	35	425	1,028	200	1,028	120	232	...	1,102	4,078
Incidence, %	5.7	0.7	1.1	0.5	2.4	6.6	1.3	...	1.9	2.1

*The 452 cases of Canellos et al[5] are not included; probably same patients as those of Arseneau et al.[1]
†Total number surveyed not reported.

with Hodgkin's disease are scarce and usually incomplete. Some authors have stated that, in contrast to the increased risk of acute leukemia, the incidence of second solid tumors in Hodgkin's disease is not higher than expected.[1-7] A survey of the literature indicates that the incidence of nonhematological cancers varies from 1.5% to 6.6% (Table 2).

Soft tissue sarcomas and squamous cell carcinomas of the skin, which appear to be related to the local effects of irradiation and originate within the radiation port, are the most frequently encountered solid tumors. Thirty-one of the 89 cases described in the literature can be categorized as such (Table 2). The remainder include different histological types with 21 reported as being epidermoid and 31 as adenocarcinomas involving various organ systems.

The 5.7% incidence of solid tumors in our group of 35 patients with Hodgkin's disease is considerably higher than the mean incidence of 2.1% derived from published reports. It is important to stress the fact that the mean latent period from treatment of Hodgkin's disease to the development of the second malignant neoplasm is 7.0 years (range, 1.5 to 19 years). Consequently, some variations in incidence will be observed depending on the median follow-up period of Hodgkin's disease population reported. In our group of patients the median follow-up period was 5.5 years, which might in part account for this higher incidence. The lack of detailed information as to type of treatment and the latent period in collected data does not permit the calculation of actual risk of solid tumor development at five and ten years. However, accepting a conservative estimate of 2.0%, solid tumor occurrence in Hodgkin's disease (Table 2) and a cancer incidence of 340/100,000 general population, it can be concluded that there is a fivefold increase in the incidence of solid tumors in Hodgkin's disease patients. In a subgroup treated with intensive irradiation and chemotherapy, the actual incidence might be even higher.

The role of the cell-mediated and humoral immunity in the pathogenesis of tumors is the subject of intensive investigations.[14,15] Major emphasis at present is placed on the defective cell-mediated immunity in the development of malignant neoplasms. Lymphomas are observed in patients with renal allografts who are given immunosuppressive therapy in order to prevent rejection.[8] It is also recognized that patients with congenital defects in T-cell function, such as immunodeficiency with ataxia and telangiectasia, and Wiscott-Aldrich syndrome, have a higher risk of developing malignant lymphoreticular neoplasms.[15,16]

The role played by the defects in humoral immunity and particularly immunoglobulins in the development of cancer is less clear. Of great interest in this context are the various reports on the association found between immunoglobulin levels and the appearance and behavior of neoplasms.

In one study salivary IgA levels were found to be two to four times higher than normal in patients with oropharyngeal and laryngeal cancers; the serum IgA level also was found to be elevated in some of these patients.[17,18] It has been suggested that the presence of high levels of immunoglobulins in patients with cancer of epithelial secretory organs may indicate a favorable response by the host to the presence of the malignant neoplasm. Conversely, depressed levels of immunoglobulin may indicate inability on the part of the body to mount a satisfactory defense against the neoplasm.[17]

Selective IgA deficiency is a fairly common condition, having a reported incidence of one in 500 to 700.[19] It has been reported in association with several diseases, mostly sinopulmonary infections and autoimmune disorders, but also certain malignant tumors, particularly of epithelial surfaces.[14,15] While the most common types of malignant neoplasm appearing in immunodeficiency disorders are lymphomas and leukemias, with congenital IgA deficiency,

69% of the subsequent malignant tumors have been epithelial in origin.[15]

So far as our two patients are concerned, in case 1 there was no detectable IgA in the serum on several occasions prior to the discovery of adenocarcinoma of the lung and kidney. In case 2 the lesions were squamous; no secretory IgA was found in the saliva, and some deficiency of serum IgA, IgG, and IgM was present. There was also evidence in this case of borderline defects in the cell-mediated immunity as demonstrated by some decrease in the percentage of circulating T-lymphocytes assayed by rosetting. We are aware that the absence of secretory IgA with detectable serum IgA is a combination not yet reported in the literature, but remains a theoretical possibility. In neither case are we able to decide if these immunoglobulin abnormalities existed prior to the diagnosis of Hodgkin's disease or occurred only after treatment.

Nevertheless they were noted at a time when the patients were in complete remission of their Hodgkin's disease. The fact that spontaneous immune deficit in Hodgkin's disease involves mainly the T rather than the B lymphocytes leads us to believe that the immunoglobulin deficits in our patients were related to previous treatment of Hodgkin's disease with irradiation and chemotherapy. Since T cells do appear to modulate the B-cell function through the "helper" and "suppressor" cell activity, it might be postulated that the immunoglobulin deficits in these patients might be an indication of increased suppressor T-cell activity.[16-19]

We believe that we can expect to see more frequent reports of solid tumor development in patients who have been treated for Hodgkin's disease or other malignant neoplasms as longevity increases following more successful treatments with various modalities. We also believe that the establishment of a registry of such cases should be seriously considered. It would be desirable to perform immune profiles on all patients with Hodgkin's disease before treatment and at measured intervals thereafter with a view to determining what, if any, predictive value such data might have to subsequent neoplastic development. This might provide important information on the role of cell-mediated and humoral immune systems on tumor induction and surveillance.

This investigation was supported in part by grant CA14144 from the Department of Health, Education, and Welfare.

Linda Wolf assisted with the preparation of this manuscript.

References

1. Arseneau JD, Sponzo RW, Levin DL, et al: Nonlymphomatous malignant tumors complicating Hodgkin's disease: Possible association with intensive therapy. *N Engl J Med* 287:1119-1122, 1972.

2. Berg JW: The incidence of multiple primary cancers: I. Development of further cancers in patients with lymphomas, leukemias, and myeloma. *J Natl Cancer Inst* 38:741-752, 1967.

3. Bonnadonna G, DeLena M, Banfi A, et al: Second neoplasms in malignant lymphomas after intensive therapy. *N Engl J Med* 288:1242-1243, 1973.

4. Brody RS, Schottenfeld D, Reid A: Multiple primary cancer risk after therapy for Hodgkin's disease. *Cancer* 40:1917-1926, 1977.

5. Canellos GP, De Vita VT, Arseneau JC, et al: Second malignancies complicating Hodgkin's disease in remission. *Lancet* 1:947-979, 1975.

6. Coleman CN, Williams CJ, Flint A, et al: Hematologic neoplasia in patients treated for Hodgkin's disease. *N Engl J Med* 297:1249-1252, 1977.

7. Neufeld H, Weinerman BH, Kemel S: Secondary malignant neoplasms in patients with Hodgkin's disease. *JAMA* 239:2470-2471, 1978.

8. Penn I: Second malignant neoplasms associated with immunosuppressive medications. *Cancer* 37:1024-1032, 1976.

9. Ezdinli EZ, Sokal JE, Aungst WC, et al: Myeloid leukemia in Hodgkin's disease: Chromosomal abnormalities. *Ann Intern Med* 71:1097-1104, 1969.

10. Moertel CG, Hagedorn AB: Leukemia or lymphoma and coexisting primary malignant lesions. A review of the literature and a study of 120 cases. *Blood* 12:788-803, 1957.

11. Razis DV, Diamond HD, Craver LF: Hodgkin's disease associated with other malignant tumors and certain non-neoplastic diseases. *Am J Med Sci* 128:327-335, 1959.

12. Slater JM, Ngo E, Lau BH: Effect of therapeutic irradiation on the immune responses. *AJR* 126:313-320, 1976.

13. Harris J, Sengar D, Stewart T, et al: The effect of immunosuppressive chemotherapy on immune function in patients with malignant disease. *Cancer* 37:1058-1069, 1976.

14. Waldmann TA, Strober W, Blaese RM: Immunodeficiency disease and malignancy: Various immunologic deficiencies of man and the role of immune processes in the control of malignant disease. *Ann Intern Med* 77:605-628, 1972.

15. Kirkpatrick CH: Cancer and immunodeficiency diseases. *Birth Defects* 12:61-68, 1976.

16. Ammann AJ, Hong R: Selective IgA deficiency: Presentation of 30 cases and a review of the literature. *Medicine* 50:223-236, 1971.

17. LoGerfo P, McLanahan S: Serum secretory IgA levels in patients with neoplastic disease. *J Surg Res* 20:481-484, 1976.

18. Brown AM, Lally ET, Frankel A, et al: The association of the IgA levels of serum and whole saliva with the progression of oral cancer. *Cancer* 35:1154-1162, 1975.

19. Waldmann TA, Blaese RM, Broker S, et al: Disorders of suppressor immunoregulatory cells in the pathogenesis of immunodeficiency and autoimmunity. *Ann Intern Med* 88:226-238, 1978.

Printed and Published in the United States of America