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Correspondence and Short Communications

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CRYOGLOBULINAEMIA TEN YEARS BEFORE ONSET OF LYMPHOMA

It is well established that genetic and acquired immune deficiency disorders predispose to lymphoid malignancy (1). However, the role of other immunologic abnormalities like cryoglobulinaemia which has been reported to occur in association with lymphomas is less clear (2). The temporal relationship between these disorders and the lymphoid malignancy is not well elucidated in the literature, although most reports suggest that the time interval more often concerns months than years and that either condition could precede the other. We now report a patient who presented with cryoglobulinaemia and leukocytoclastic vasculitis 10 years prior to the clinical onset of lymphoma.

Case report. A 35-year-old traffic policeman first presented in 1981 with a two-year history of intermittent 'bruising' in the legs with more recent involvement of the arms and trunk, and intermittent bipedal edema. On examination he had macular purpuric and petechial lesions, mostly around hair follicles. There was no enlargement of lymph nodes or hepatosplenomegaly. He had normal blood counts, coagulation profile, immunoelectrophoresis, platelet function and C3 complement levels. Coomb's test, liver function tests, stool screening, α-fetroprotein and CEA were all negative. A skin biopsy showed leukocytoclastic vasculitis and the serum was positive for cryoglobulins. The patient declined a bone marrow biopsy. He was followed up and had 6 months later a single episode of hematemesis. Upper and lower gastrointestinal endoscopy, chest x-rays, ultrasound examination of abdomen were all normal and blood tests were non-contributory to the cause of the bleeding. The patient remained well but was then lost to the follow-up. He returned to the clinic 7 years later, in 1988. His previous symptoms remained and he had now increasing bipedal edema. Apart from the leg edema and the skin lesions as previously described, clinical examination was again unremarkable. His blood pressure, however, was raised with a value of 170/100 mm Hg. ESR was 78 mm/h, IgM was raised at 6.24 g/l, rheumatoid factor was positive at 1:1 280, C3, C4 and CH50 were all low. Protein electrophoresis showed monoclonal gammopathy of IgM kappa type. LDH levels were at the upper limit of normal and cryoglobulins were again positive. Serum albumin was 26 g/l and 24-h urine protein was 10 g. Chest x-rays and ultrasound examination of the abdomen were unremarkable. In view of the nephrotic syndrome, renal biopsy was performed and showed membranoproliferative gomerulo nephritis with features of cryoglobulinaemic glomerulopathy. The patient was commenced on anti-hypertensive therapy. The next significant development was in March 1991, 10 years after his first presentation, where he developed a symptomatic left-sided pleural effusion. He had no constitutional symptoms of lymphoma. LDH was elevated to 9 297 units, cryoglobulins were still positive, and again monoclonal gammopathy of IgM kappa type was seen. CT scans of chest and abdomen showed extensive mesenteric and upper abdominal lymph nodes. Pleural biopsy showed intermediate grade non-Hodgkin's lymphoma of the large non-cleaved cell type. Bone marrow biopsy was normal. The conclusion was that he had stage IVA non-Hodgkin's lymphoma and he received combination chemotherapy using the VECOP-B regimen (etoposide, epirubicin, cyclophosphamide, vincristine, cisplatin and bleomycin) on a weekly basis for a total of 12 weeks, at the end of which he achieved complete remission. There was minimal residual pleural thickening on the left side. He has remained in remission now for 14 months but recent skin biopsy still shows leukocytoclastic vasculitis and cryoglobulins remain positive. He also has mild renal dysfunction with creatinine of 123 μmol/l and continues to have nephrotic syndrome, though urinary protein loss now measured at 5.6 g/24 h is less than what it used to be.

Discussion. Cold induced precipitation of proteins was first described by Wintrobe & Buell in 1933 (3), and the term cryoglobulins was introduced by Lerner et al. in 1947 (4) to describe this subset of immunoglobulins. We now know that the cryoglobulins can be divided into three types—monoclonal, mixed and polyclonal varieties (5). Cryoprecipitation is known to occur both as an isolated phenomenon with no identifiable underlying disease (6) and in association with a number of disease states, mainly infectious, autoimmune and lymphoproliferative (2). The clinical significance of the cryoglobulins was systematically analyzed by Brouet et al. in 1974 and they reported the association of type I and II with immunoproliferative, and type III with autoimmune disorders (2). In their study, 6 out of 86 patients went on to develop low-grade lymphomas, though the time interval is not clear. They also reported renal involvement which was found more commonly in type II and type III. Our case illustrates several of the characteristic features of type II cryoglobulinaemia, particularly the purpuric lesions. Glomerulonephritis is a well-known feature, sometimes leading to renal failure, and the characteristics have been well described (7). Complement activation by the immunoglobulins leading to reduced levels has been well described (8). Cryoglobulinaemia is also associated with rheumatoid factors, in particular type II (8), as in our case. Extensive review of literature with relevance to our case suggests that the following questions remain unanswered:

- The mechanism linking cryoglobulinaemia and lymphoma.
- Identification of risk factors for development of lymphoproliferative disorders.
- Defining the follow-up of these cases and steps needed for early identification of malignant disorders.

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SERUM CONCENTRATIONS OF INSULIN-LIKE GROWTH FACTOR 1 IN COLONIC NEOPLASIA

Several recent studies have focused attention on a possible role of hormones and growth factors in the initiation and growth of colonic neoplasia (adenomas and carcinomas). Specifically, the increased incidence of colonic neoplasia in patients with acromegaly (1–6), a disorder of growth hormone overproduction by a pituitary adenoma, strongly suggests that excess of either growth hormone itself or insulin-like growth factor 1 (IGF-1; synonym: somatomedin C), a polypeptide growth factor whose production is stimulated by growth hormone, can lead to development of colonic adenomas or cancer. These observational studies are supported by biochemical studies, indicating that colon cancer cell lines possess receptors for IGF-1 and that IGF-1 can stimulate mitogenesis and growth of these neoplastic cells (7, 8). As a preliminary step in the exploration of a potential role for IGF-1 in the pathogenesis of colonic neoplasia in the non-acromegalic general-population, we measured the circulating concentrations of this hormone in 334 healthy subjects who underwent complete colonoscopy to assess the presence or absence of colon polyps and colon neoplasia.

Material and Methods. All healthy adult men and postmenopausal women who were undergoing colonoscopy at Walter Reed Army Medical Center from 1984 through 1987 because of occult blood in the stool or because of possible colonic polyps seen on barium enema were solicited to participate in this study. Subjects were excluded if they had a history of colonic adenomas or cancer, familial polyposis, inflammatory bowel disease, malabsorption, alcoholism, recent weight loss, and renal or hepatic disease. In addition, 9 other subjects with cancer in pedunculated colonic adenomas were also included; 8 of these patients were identified during a concurrent study of colonic adenoma recurrence. All subjects underwent complete colonoscopy with biopsy of all polyps; subjects with incomplete colonoscopy or inadequate biopsy specimens were excluded. Histologic evaluation was initially performed by the Department of Pathology, Walter Reed Army Medical Center, with re-evaluation and confirmation by one of the authors (LHS) for 80 subjects, including all those with diagnoses of carcinoma in a pedunculated adenoma, carcinoma-in-situ, and high grade or severe dysplasia. Based on results of colonoscopy, subjects were classified into one of three categories: control, adenoma, or carcinoma. Classification as a control required colonoscopy complete to the cecum, biopsy of all polyps visualized, and no pathologic diagnosis of adenoma or carcinoma. The finding of hyperplastic polyps was not considered in the assignment of subjects to diagnostic categories. Blood samples were obtained from all subjects between 07.00 and 09.30 h after an overnight fast. Blood was allowed to clot at room temperature, centrifuged, aliquotted into air-tight vials, stored at −80C for 3–7 years, and subsequently shipped on dry ice for measurement of IGF-1 (Endocrine Sciences, Tarzana, CA, USA). After acid-ethanol extraction, serum samples were assayed for IGF-1 by double antibody radioimmunoassay using an antibody directed against IGF-1 57–70. Assay sensitivity is 3.3 pmol/ml with interassay variation of 13%. Statistical analysis was performed using Wilks-Shapiro test for normality, analysis of variance, student's t-test, and χ^2 test. This project was approved by the Clinical Investigation and Human Use Committees of Walter Reed Army Medical Center, and all subjects provided written, informed consent.

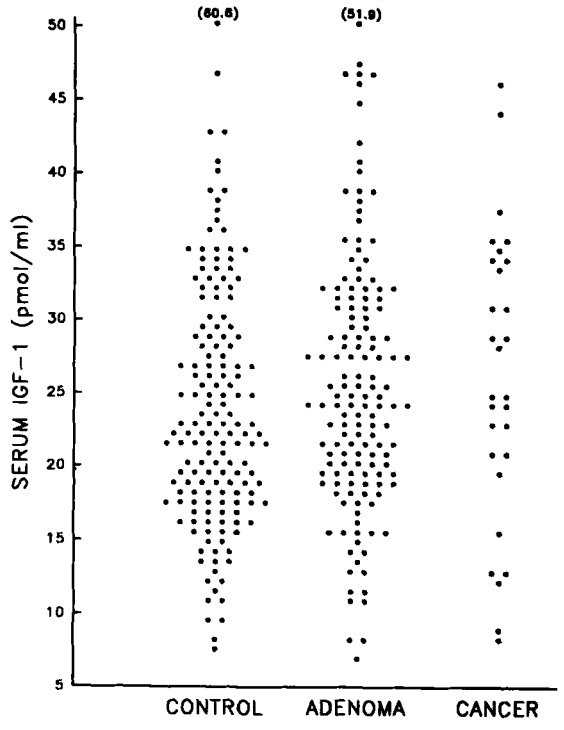

Figure. Serum IGF-1 concentrations in 334 subjects according to diagnostic category. The IGF-1 concentrations of two subjects whose values were off-scale are indicated in parentheses.

Results. The mean ages in the 3 diagnostic groups were slightly but significantly different (control = 58.4 years, adenoma = 60.3,

Table

Serum IGF-1 concentrations in colonic neoplasia

	Serum IGF-1 (pmol/ml)		Frequency of high serum IGF-1 (%)	
Control (n = 159)	24.0 ± 0.7		2.5	
	↑ NS	NS	↑ NS	NS
Neoplasia (n = 175)	↓ 25.7 ± 0.7		↓ 6.3	
Adenoma (n = 146)	25.6 ± 0.7		6.2	
Carcinoma (n = 29)	26.2 ± 1.8		6.9	

Serum IGF-1 concentrations are mean ± SEM. Neoplasia group is a combination of adenoma and carcinoma groups. High serum IGF-1 is defined as greater than 40.3 pmol/ml (mean + 2 SD of controls). NS indicate that values connected by arrows are not significantly different (ANOVA or student's t-test for serum IGF-1 and χ^2-test for % high serum IGF-1).