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Vitamin A and Retinol-binding Protein in Patients with Myelomatosis and Cancer of Epithelial Origin

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Abstract—*Serum vitamin A and retinol-binding protein (RBP) concentrations were measured in patients comprising 53 myeloma and 28 epithelial cell cancer cases. Vitamin A levels in these patients were found to be significantly lower than those in the 30 healthy subjects, the effect being more marked in the patients with cancer of epithelial origin. The serum concentrations of retinol-binding protein (RBP) fell in parallel with vitamin A in the epithelial cancer patients, while the RBP concentrations remained unaffected in the patients with myeloma, suggesting that the underlying factor for resulting low vitamin A levels may be different in these two groups of patients.*

INTRODUCTION

VITAMIN A has a considerable controlling influence on epithelial differentiation [1, 2]. If this vitamin is deficient, differentiation switches in the pathway leading to keratinized squamous cells which replace normal epithelium, a process termed squamous metaplasia [3, 4]. Of particular concern in recent years is the possible association between vitamin A deficiency and cancer of epithelial origin [5]. In animals vitamin A deficiency has been shown to increase susceptibility to chemical carcinogenesis in the respiratory tract [6], skin [7], bladder [8] and colon [9]. Large doses of natural retinoids have been reported to abolish this enhanced susceptibility [10–12]. Furthermore, both biochemical [13–15] and epidemiological [16, 17] studies have provided evidence to support a link between vitamin A deficiency and cancers of epithelial origin in man.

However, there appears to have been no report made concerning vitamin A status in patients with cancer of non-epithelial origin. The present paper reports a retrospective study in which serum levels of vitamin A and retinol-binding protein (RBP) were measured in patients with a malignancy of the reticulo-endothelial system, i.e. myelomatosis. This study also included patients with cancer of epithelial origin at various sites in order to provide confirmation of previous studies [13, 15].

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MATERIALS AND METHODS

Patients

A total of 53 (29 males, 24 females) patients with myeloma were studied. Their ages ranged from 57 to 86 yr, with a mean of 69. The paraprotein types of these patients were found to be 22 with IgG (K); 9, IgG (L); 6, IgA (K); 5, IgA (L); 6, IgM (K); 2, IgM (L); 2, Bence Jones (L); and 1 with Bence Jones (K). At the time of this investigation these patients were being treated with chemotherapy, including melphalan and cyclophosphamide. The result of these patients were compared with those of 28 (10 males, 18 females) cases with cancer of epithelial origin at various sites, including endometrium, lung, bronchus, bladder and breast. Their ages ranged from 50 to 79 yr, with a mean of 62. These patients were undergoing treatment with 5-fluorouracil, cyclophosphamide, vincristine and methotrexate. As far as could be determined, all patients had taken a similar diet. Thirty healthy subjects (29 males, 1 female) were also included in this study; their ages ranged from 38 to 65 yr, with a mean of 50.

In order to determine whether the cytotoxic agent melphalan had an effect on vitamin A levels, the serum concentrations of this vitamin were measured at daily intervals for 30 days in a patient with myeloma following intravenous

administration of a large single dose (140 mg/m^2) of the drug.

Vitamin A in the serum was determined by a modification of the fluorometric method of Hansen and Warwick [18] and Van Steveninck and De Goeij [19]. In this method the fluorescence was measured at an emission wavelength of 550 nm, where interference from carotenoids was found to be virtually zero. Serum RBP was determined by the single radial immunodiffusion technique [20] using LC-partigen immunodiffusion plates (Behring diagnostics, Hoechst, U.K.).

RESULTS

The results of the vitamin A and RBP assays are shown in Table 1. Compared to healthy subjects, the serum vitamin A levels were found to be significantly lower in all patients both in those with myeloma and those with cancer of epithelial origin. However, this effect appeared to be more marked in the latter group than in the former. Patients with cancer of epithelial origin were divided into groups according to the site of the cancer (Table 2). It was of interest that the patients with lowest serum vitamin A levels were represented by the endometrial cancer group, and the highest vitamin A levels were found in the patients with breast cancer involving ductular epithelium. Intermediate between these two values was the serum vitamin A of the patients with cancers of the bladder, lung and bronchus. The serum RBP content in these patients followed a similar pattern, although the difference between the groups was not found to be statistically significant except only between the patients with endometrial and breast cancers. Low serum vitamin A levels were found to be associated with reduced serum RBP concentrations in the patients with cancer of epithelial origin but not in the patients with myeloma, when compared with normal healthy subjects (Table 1). The reduced serum vitamin A levels in patients with myelomatosis was not found to be correlated with the heavy or light chain paraprotein type of the disease. Patients with macroglobulinaemia (IgM paraproteinaemia) revealed a pattern similar to that seen in myeloma. Analysis of serum vitamin A in a patient with myeloma given a single megadose (140 mg/m^2) of the cytotoxic drug melphalan intravenously did not reveal any correlation between vitamin A levels and the drug used. There was, in fact, a small but constant upward trend of vitamin A levels observed in this patient.

Table 1. *Serum concentrations of vitamin A and retinol-binding protein (RBP) in patients with myeloma and with cancer of epithelial origin*

Subjects	No.	Vitamin A (μg/100 ml)	RBP (mg/100 ml)
Healthy controls	30	85.3± 2.9	3.3± 0.1
Myeloma patients	53	59.8± 3.7*	3.5± 0.2
Epithelial cancer patients	28	36.5± 2.8**	2.5± 0.1**

Each value represents the mean of the number of subjects shown with ± S.E.M. Statistical differences between the control subjects and cancer patients: *$P < 0.01$; **$P < 0.001$.

DISCUSSION

In previous studies [13, 15] patients with bronchial carcinoma had been reported to be associated with lower serum concentrations of vitamin A than those with non-malignant lung diseases or healthy subjects. Not only the carcinoma of bronchi, but also the carcinoma of oral cavity and oropharynx, have been found to be accompanied by low serum vitamin A levels [14].

The present study in a small number of cases demonstrated that patients with carcinoma of the other epithelial sites, such as the bladder, endometrium and breast, have also had reduced serum vitamin A levels. These low vitamin A levels were associated with reduced serum RBP concentrations, confirming our previous

Table 2. *Serum vitamin A and retinol-binding protein (RBP) levels in relation to the site of epithelial cancer*

Site of epithelial cancer	No. of patients	Vitamin A (μg/100 ml)	RBP (mg/100 ml)
Endometrium	4	25.2 ± 2.2**	2.0 ± 0.1*
Lung and bronchius	7	32.7 ± 1.8*	2.4 ± 0.2
Bladder	5	34.0 ± 2.0*	2.6 ± 0.1
Breast	12	47.4 ± 3.1	2.7 ± 0.2

Each value represents the mean of the number of patients shown with ± S.E.M. The statistical difference between the patients each with cancer of the endometrium, lung and bronchius, or bladder and those with breast cancer: *$P < 0.01$; **$P < 0.001$.

findings [15] in patients with bronchial carcinoma.

Vitamin A is transported in the plasma from the liver stores being bound with RBP [21], which in turn is complexed with prealbumin. It is, therefore, possible that the depressed serum concentration of vitamin A in patients with cancer of epithelial origin is due to impaired mobilization of the vitamin from the liver.

Our present study has also indicated that myelomatosis, involving the reticulo-endothelium, is similarly associated with low serum vitamin A levels, although not as marked as in the patients with cancer of epithelial origin. However, unlike the latter cases, the patients with myelomatosis appear to show normal serum RBP concentrations, and this is true irrespective of the stage of the disease and paraprotein class. It is also of interest that the prealbumin levels in myeloma patients do not appear to be significantly reduced [22] in contrast to other malignancies. It appears, therefore, that both groups of cancer patients provide biochemical evidence of vitamin A deficiency, but the underlying causes for this deficiency may be different.

It is possible that there is an increased requirement for vitamin A in patients with myeloma due to either the disease or the treatment with drugs such as melphalan. A competitive uptake of vitamin A by neoplastic cells has also been postulated. However, the likelihood of melphalan affecting serum vitamin A levels is rather unlikely since our findings demonstrated no effect, even after the administration of very large single dose (140 mg/m^2) of melphalan to a patient with myeloma. There was, in fact, a small but constant upward trend of vitamin A levels demonstrated in this patient.

Further work is certainly warranted to elucidate the possible cause of vitamin A deficiency in patients with myelomatosis.

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