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Could the use of appropriate diet help in the prevention of multiple myeloma?

Dear Editor,

The severity of the monoclonal gammopathy of undetermined significance (MGUS) is based on data from a large epidemiologic study with a median follow-up of 15.4 years, showing constant rate (1% per year) of progression of MGUS to multiple myeloma. Patients were at risk even after 25 years or more of stable MGUS, making life-long follow-up necessary [1,2].

Occurrence of "M" component in the sera of patients with psoriasis, or psoriatic arthritis, like in MGUS, has been reported [3], and it was stressed that these patients can sometimes develop multiple myeloma [4]. We tested serum IgA and IgG immunoreactivity to 3 food constituents and the presence of MGUS in an 83-year-old patient with psoriatic arthritis diagnosed in 2000, by ELISA and by electrophoresis and immunofixation. Cow's milk proteins (CMP) (ICN Biomedicals, Inc. Costa Mesa, USA), phytohemagglutinin P (PHA) (INEP Zemun, Serbia) and gliadin (Binding Site, Birmingham, UK) were used as antigens for ELISA tests.

The results indicated much enhanced IgA and IgG immunoreactivity to CMP. Analysis of the patient's serum by electrophoresis and immunofixation revealed the presence of "M" component (monoclonal IgG (λ) immunoglobulin; Figure 1A). When the patient learned about his enhanced immunoreactivity to CMP, he decided not to consume food with CMP. A month and half after the start of CMP-free diet, analysis of serum proteins was carried out. At that time, the patient had not taken any immunosuppressive drugs.

Serum electrophoresis revealed disappearance of the "M" component (Figure 1B). Also serum anti-CMP IgG dropped from 892 AU/ml to 0 AU/ml (anti-CMP IgA also dropped from 240 AU/ml to 0 AU/ml). Besides, concentrations of total serum proteins and of IgG were diminished after the CMP-free diet (Table 1).

Our results are in accordance with the data from only one report dealing with a possible link between disappearance of MGUS and gluten-free diet [5]. In conclusion, this analysis indicates the need for new research aiming at answering whether special food restriction diet for individuals with enhanced immunity to some food constituent(s) would help manage the now non-curable MGUS.

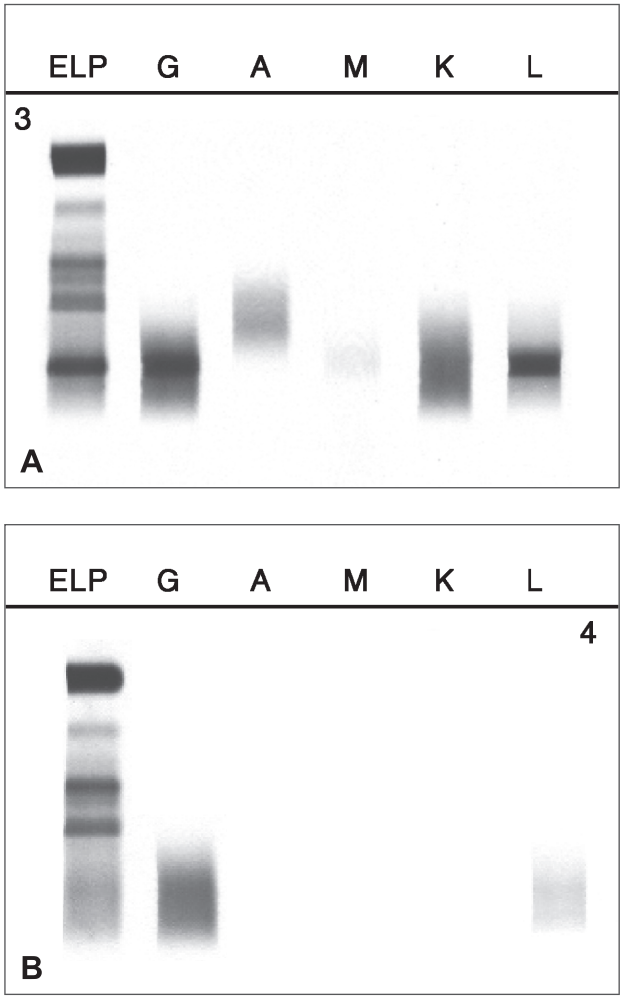

Figure 1. Serum protein electrophoresis and immunofixation. **A:** "M" component before CMP-free diet; **B:** disappearance of "M" component after CMP-free diet.

Table 1. Proteins in patient's serum before CMP-free and after CMP-free diet

	Date		
Test	*6/24/ 2008 Before CMP-free diet*	*8/26/ 2008 After CMP-free diet*	
Electrophoresis	*With "M" component*	*Without "M" component*	*Normal range values*
IF "M" component	IgG (λ)	–	–
Total IgG (g/L)	17.8	11.23	7.0-16.0
Total IgA (g/L)	2.21	2.95	0.7-4.0
Total IgM (g/L)	0.51	0.33	0.4-2.3
Albumins (g/l)	42	40	35-50
Total proteins (g/l)	73	69	65-82
Anti CMP IgG (AU/mL)	892	0	<38.83
Anti CMP IgA (AU/mL)	240	0	<11.32
Anti PHA IgG (AU/mL)	50	100	<128
Anti PHA IgA (AU/mL)	100	84	<248
Anti gliadin IgG (IU/mL)	4.1	nd	<5.83
Anti gliadin IgA (IU/mL)	2	nd	<3.46

IF: immunofixation, CMP: cow's milk protein

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Prolonged disease free survival with aggressive adjuvant chemotherapy in a case of large cell neuroendocrine carcinoma of the uterine cervix

Dear Editor,

Large cell neuroendocrine carcinoma (LCNEC) of the uterine cervix is a rare malignancy comprising about only 0.6% of all cervical tumors, with a highly aggressive biologic behavior and a clinical course frequently characterized by early high regional recurrence rate and widespread hematogenous metastases [1]. Many treatment modalities have been used, however prognosis remains poor for both early and advanced disease. Our experience is derived from a case of a 60-year-old patient with large cell neuroendocrine cervical tumor treated with radical surgery, followed by adjuvant chemotherapy with cisplatin and etoposide (PE) for 6 courses and consolidation radiotherapy. The patient remained free of tumor recurrence for 14 months. Metastatic disease occurred in the lungs and liver and was first treated with PE and then with cisplatin/irinotecan without response and the patient succumbed to her disease 18 months after initial diagnosis.

The basis of treatment of LCNEC of the uterine cervix is derived from the therapy of cervical small cell neuroendocrine carcinoma (SCNEC) and small cell lung tumors. Initial surgical therapy in the form of radical hysterectomy with bilateral salpingo-oophorectomy and lymph node dissection for the treatment of LCNEC at early stages appears to be crucial predisposing to a better prognosis, as long-term disease-free survival has been reported only in patients with early-stage disease treated with surgery [2]. Chemotherapeutic regimens used for the treatment of LCNEC usually follow those of cervical and pulmonary SCNEC. Regimens containing cisplatin and etoposide and vincristine, adriamycin, cyclophosphamide (VAC) offer survival advantage and are more frequently used [3]. Regarding the use of radiation therapy, most clinicians prefer adjuvant radiation even in early-stage disease. However, several studies have failed to support the use of adjuvant radiation, as patients receiving adjuvant radiation tended to have a poorer prognosis in comparison with patients receiving only adjuvant chemotherapy, while adjuvant chemoradiation did not result in a better outcome when compared to adjuvant chemotherapy alone [3,4].

According to our experience and the conclusions

of other studies it seems that patients with LCNEC of the uterine cervix treated aggressively with adjuvant chemotherapy might obtain a prolonged disease-free interval since the role of radiotherapy is controversial and warrants further investigation. Future reports and studies may augment our experience and help improve patients' outcome by establishing better treatment modalities.

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E-cadherin, b-catenin and topoisomerase II expression in rhabdomyosarcomas

Dear Editor,

E-cadherin, b-catenin and topoisomerase IIa show increasing interest and have been subjected to extensive investigation regarding their expression and possible role in prognosis in soft tissue sarcomas [1-3]. We investigated the expression of these 3 molecules in a small series of 6 primary, nonmetastatic rhabdomyosarcoma (RMS) patients, median age 44 years. In 3 patients the tumor location was in the pelvis, in 2 patients in the orbit and in 1 patient in the cervical spine. The median tumor size was 122 mm (range 6-220). All RMSs were treated surgically with radical tumor excision. Adjuvant treatment was given to 3 patients (2 patients combined chemoradiotherapy and one postoperative radiotherapy).

Immunostaining was performed on formalin-fixed, paraffin-embedded tissue sections using the EnVision System (DAKO Corp, Netherlands), and the monoclonal antibodies E-cadherin (CM170B, Biocare Medical, California), b-catenin (DBS, Menarini, Hellas) and topoisomerase IIa (Ki-S1, DAKO,). Briefly, 4μm-thick tissue sections were deparaffinized in xylene, rehydrated through graded concentrations of alcohol and heated in a microwave oven for 2 cycles of 15 min each at 300W, in citrate buffer, for antigen retrieval. Endogenous peroxidase activity was blocked with H_2O_2 solution in methanol (0.01M) for 30 min. After washing with PBS for 5 min, the primary antibodies CM170B (dilution 1:50), b-catenin (dilution 1:50) and topoisomerase IIa (dilution 1:50) were incubated (30 min at room temperature). Then, the slides were washed for 10 min with PBS and were visualized with the EnVision system (DAKO) using diaminobenzidine tetrahydrochloride as a chromogen (Sigma Fast DAB tablets, St. Louis, Mo). Finally, all sections were counterstained with hematoxylin. As a negative control, the first antibody was substituted with normal mouse immunoglobulin of the same class. A semiquantitative method was used for the evaluation of E-cadherin, b-catenin and topoisomerase IIa. A level of over 20% cell staining was regarded as the cut-off level of a tumor expressing the above markers.

None of the examined RMSs showed E-cadherin expression. Similarly, none of the RMSs had positive nuclear b-catenin expression. Cytoplasmic b-catenin expression was seen in 2 patients. Both of them had strong expression of cytoplasmic b-catenin of 40% and 100%, respectively. Topoisomerase IIa was expressed in all but one RMSs. All but one patient had strong expression (range 50-90%). The two patients that had positive b-catenin staining had high topoisomerase IIa expression.

In RMSs absence of E-cadherin expression has also been reported by Sato et al. who found that only 1 out of 12 RMSs had E-cadherin expression [1]. This

absence can indicate either no involvement of this molecule in the constitution of RMSs architecture, or reflect the aggressive behavior of these neoplasms. Charrasse et al. showed a decrease in the expression of cadherins family in all RMS-derived cell lines compared to control cells [4]. Our literature search did not recognize any published data reporting on b-catenin expression in RMSs. Finally, Coffin et al. have found that topoisomerase IIa expression decreased after therapy and correlated with cytodifferentiation and survival in the botryoid subtype [5]. In conclusion, the present report provides evidence regarding the expression of E-cadherin, b-catenin and topoisomerase IIa in a small RMS population. Further evidence through larger investigations is needed in order to confirm our results and to provide additional information of their possible role in disease progression.

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An unusual case of recurrent non-Hodgkin's lymphoma presented with massive ascites, peritoneal involvement and elevated CA-125 level

Dear Editor,

Simultaneous occurrence of massive ascites and non-Hodgkin's lymphoma (NHL) has been rarely documented [1]; only one case with peritoneal NHL and elevated CA-125 levels has been previously documented in the English medical literature [2]. Several studies suggested that CA-125 levels in NHL patients may be helpful in predicting disease activity [3,4].

A 70-year-old male was admitted to our hospital with a history of stuffiness in March 2002. Stage IE diffuse large B cell NHL of the nasopharynx was confirmed from a biopsy taken from a polypoid mass which extended into the posterior end of the nasal cavity. The tumor was Ki-67 (+) in 70% of cells, CD20 (+) and CD3 (–). One cycle of chemotherapy \with cyclophosphamide and vincristine was administered along with radiotherapy (4500cGy) to the nasopharynx during a one-month period. Cervical, thoracic and abdominal CT scans and biochemical parameters showed complete response (CR).

One year later he was hospitalized with 2-month history of fatigue, anorexia, and progressive enlargement of waist circumference. On physical examination, he had massive ascites and decreased respiratory sounds of the lung bases bilaterally. There was no lymphadenopathy. Splenomegaly (3 cm) was noted in the midclavicular line. The initial lab work-up showed white blood cell (WBC) count 27,400/m^3, hemoglobin 13.7 g/dL, hematocrit 40%, platelet count 95,000/m^3, erythrocyte sedimentation rate 65 mm/h, urea 124 mg/dL (10-50), creatinine 1.86 mg/dL (0.50-1.50), uric acid 16.9 mg/dL (3.4-7.0), sodium 127 mEq/L (135-145) potassium 5.3 mEq/L (3.5-5.0), LDH 1271 U/mL (98-192), and CA-125 857 U/mL (1.7-32.0). Other lab tests were within normal range. The patient was hydrated and allopurinol therapy was initiated. These parameters returned to normal ranges on day 15.

On the 5th day of hospitalization, WBC increased to 51,400/m^3 and peripheral blood smears revealed atypical mononuclear cells that increased from 20% to

74%. On immunohistochemistry (IHC), Sudan-Black and PAS stainings were negative. CD5 (+) clonal B cell population which weakly expressed CD23 was detected on peripheral blood. Ascitic fluid was exudate. WBC count was 21,000/mm^3 and 90% of the cells were atypical mononuclear cells. Cytology of the ascitic fluid showed a large number of immature monomorphic lymphoid cells, attributable to NHL infiltration. Thorax and abdominal CT scan revealed bilateral pleural effusion, splenomegaly, infarction at the lower and middle region of spleen, multiple intraabdominal conglomerated nodal packs, massive ascites, and diffuse peritoneal implants.

On the 10th day of admission combination chemotherapy with cyclophosphamide 750 mg/m2 and vincristine 1.4 mg/m2, both on day 1, was administered. Doxorubicin and prednisone were not administered due to cardiac dysfunction, urate nephropathy and hematemesis. The initial WBC count of 64,000/mm3 decreased to 7,100/m3 on day 10 of chemotherapy. CA-125 level dropped from 857 to 205 U/mL on day 20. Waist circumference decreased considerably. Six cycles were administered with complete clinical and laboratory remission. He remains in CR 6 years thereafter.

Peritoneal involvement in NHL is about 1-3% [1]. Because the omentum lacks lymphoid elements, lymphomatous infiltration is uncommon. In a study, peritoneal involvement has been found in only 4 patients [4]. In studies with respect to NHL and CA-125, CA-125 has been considered to be an indicator of peritoneal stimulation evoked by tumoral invasion rather than a direct tumoral product. It has also been reported as an important marker in monitoring treatment and follow-up of patients with NHL and coexisting peritoneal involvement and ascites [5], in staging and assessing tumor activity and in predicting decreased survival. In our case, pretreatment CA-125 levels were fairly elevated (857 U/mL), gradually decreased and returned to normal on the 3rd month of treatment.

In patients with NHL who have massive ascites and elevated CA-125 level, recurrent NHL with peritoneal involvement should be considered in the differential diagnosis.

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