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Clinical Study

IgA Anticardiolipin in Patients with Gastroenteric Tumor

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Recently the presence of antiphospholipid antibodies in patients with cancer has been demonstrated, suggesting an involvement of autoimmune response in neoplastic conditions. The presence of antiphospholipid antibodies in tumor disease is highly correlated with the risk of developing thrombotic complications, which represents a significant cause of morbidity and mortality in cancer patients. Interestingly, it has been highlighted that high levels of IgM and IgG anticardiolipin antibodies are more often produced in patients with gastroenteric tumor than in patients with either ovarian or breast tumor. Thus far, there are no data looking into the role or measurements of IgA in patients with solid cancer. Our preliminary results, in this study, demonstrate that testing only for IgG and IgM anticardiolipin antibodies may increase the incidence of false positive because 44% who were IgA positive and IgG and IgM negative had high titres of CA19.9 and CEA. We suggest that taking into account the role of IgA could substantially improve the detection of antiphospholipids antibodies in subjects with solid cancer, and this detection may allow us for better prevention and management of thrombotic complications in these patients.

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1. Introduction

The association of antiphospholipid antibodies (aPLs) with different autoimmune pathologies and particularly with antiphospholipid syndrome (APS), characterized by arterial and venous thrombosis and recurrent pregnancy loss, has been widely reported [1–4]. The immunoassay currently used for the diagnosis and monitoring of these pathologies is the IgM and IgG anticardiolipin (aCL) test. It has been demonstrated that IgA aCL is also associated with APS, but its routine measurement does not improve the operative characteristics of other aCL tests, and therefore, it is not recommended to date [5, 6]. Nevertheless, the prevalence of IgA aCL is high in patients with pregnancy morbidity [7], in patients with Henoch-Schonlein purpura [8, 9], and in African American patients with systemic lupus erythematosus [10]. Moreover, while no significant differences of IgG aCL levels have been found between the Kawasaki disease and febrile patients, IgM and IgA aCL were significantly higher in patients with acute Kawasaki disease compared to febrile children [11]. In addition, samples from atherosclerosis patients with low IgA aCL level presented high levels of IgA anti-beta 2-GPI [12]. There is also evidence in the origins and specificities of IgG, IgM, and IgA aCL [13]. Moreover, clinical manifestations of patients with IgA aCL differ from those of patients with IgG aCL, showing a higher association of IgA aCL with skin manifestations and small vessel vasculitis [14] (i.e., cutaneous leukocytoclastic vasculitis) [15] and with infectious diseases such as mumps [16]. Recently, the presence of aPL in patients with cancer has indicated an autoimmune response in neoplastic conditions [17, 18]. The presence of these antibodies in the diagnosis of tumor disease is correlated with high risk of developing thrombotic complications [19] which represent a significant cause of morbidity and mortality in cancer patients. Interestingly, it is has been highlighted that high levels of IgM and IgG aCL antibodies are produced only in the patients affected with gastroenteric tumor that have high level of CA19.9+ and CEA-CA19.9+, and not in patients with ovary and breast tumor [20]. So far there are no data regarding the possible role and production of IgA aCL in the patients with gastroenteric tumor, especially for the role of IgA

immunization in the intestinal mucosa. In fact, bacteria colonize the intestine shortly after birth and thereafter induce the production of protective IgA antibodies [17, 21]. Therefore, the aim of the present study was to investigate the presence of IgA aCL in patients affected with gastroenteric tumor and to compare the results with those of IgM and IgG aCL.

2. Materials and Methods

2.1. Materials. CL was obtained from Sigma Chemical Co. (St. Louis, Mo, USA). The IgA, IgG, IgM–CL kits were generously donated by of Alfa Wassermann (The Netherlands).

2.2. Patients. Blood samples of patients with gastroenteric tumor disease were collected upon diagnosis from the "Laboratorio Centralizzato di analisi chimico-cliniche Ospedale Silvestrini, Perugia" over an 18 month period. A very selective population was chosen. From all patients (160), only those with tumor disease, without a history of autoimmune disease and tromboembolic damage and with normal hematological parameters, were studied (23 patients). The population was composed of 10 males and 13 females average age was 64 years (range 55–73 years). The control group was composed of 25 healthy blood donors: 15 males and 10 females, average age 37 years, (range 18–56 years). The serum samples were stored at −20°C until used.

2.3. Serum Assays for CEA, CA19-9, CA125, and CA15.3. Serum CEA and CA19-9 were measured by using the chemiluminescence immunoassay on the ADVIA Centaur system (Bayer Healthcare Diagnostics Division, Tarrytown, NY, USA). The recommended cutoff levels of serum CEA and CA19-9 were 5 ng/ml and 37 U/ml, respectively.

2.4. IgA-, IgM-, and IgG-aCL Evaluation. Measurements of IgA- IgG- and IgM-aCL were done by kits for Elisa test (Alfa Wassermann, Alanno, Pescara, Italy) as previously reported [20] and have been repeated three times; similar results were obtained.

3. Results

Of 23 positive tumor marker patients analyzed, 6 were found to be CEA positive, 9 CA19.9 positive, and 8 CEA-CA19.9 positive. Of CEA positive patients, 50% were males and 50% females, of CA19.9 positive patients, 44% were males and 56% females, and of CEA-CA19.9 positive patients, 37% were males and 63% females (see Figure 1). Of the total patients, 15 had low, moderate, or high aCL (see Figure 2). The IgG and IgA aCL never had low titre. The IgM aCL antibodies had consistently low titre and were positive only in 5 patients, 3 of which in association with IgG and 2 with IgG-IgA. Considering patients with only one positive antibody, 3 were IgG positive and 4 were IgA positive. The IgA patients were associated with IgG in 3 patients and with IgM-IgG in 2 patients.

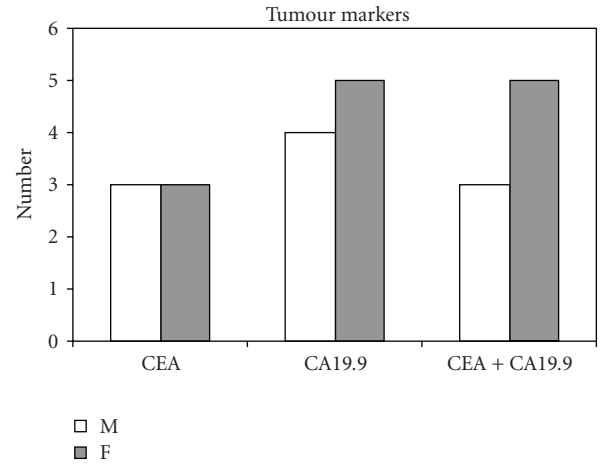

Figure 1: Tumor marker positive patients. The data are expressed as number of males and females positive patients in the total patients under study (23 patients).

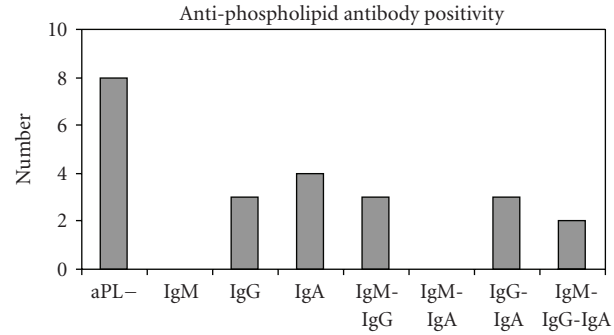

Figure 2: Antiphospholipid antibodies in tumor patients. The data indicate the number of patients with IgM, IgG and IgA anticardiolipin (aCL) antibodies.

Among patients who were positive for CEA or CA 19.9, but not both, 67% were aPL+, whereas among patients who were both CEA and CA 19.9 positive, 50% were aPL+. In more detail, for patients who were only CEA positive, the following antibody percentages were found: IgG (1/6; 17%), IgA (3/6; 50%), and the combination of IgG, IgA, and IgM (1/6; 17%, see Figure 3(a)). For patients who were CA 19.9 positive only, the following percentages were found: IgG (1/9; 11%), IgA (1/9; 11%), for the combination of IgM and IgG (1/9; 11%), IgG and IgA (2/9 22%), and for the combination of IgM, IgG, and IgA (1/9; 11%, see Figure 3(b)). Finally, for the patients who were both CEA and CA19.9 positive, the following antibody percentages were found: IgG (1/8 13%) and the combination of IgG and IgA (1/8; 13%), and for IgM and IgG (2/8; 25%, see Figure 3(c)).

These preliminary results reveal a number of interesting findings: looking among those patients with aPL+ (15/23; 65%), 60% were IgA positive and strikingly of these subjects, 44% were highly IgA positive but not IgM or IgG (see Figure 4).

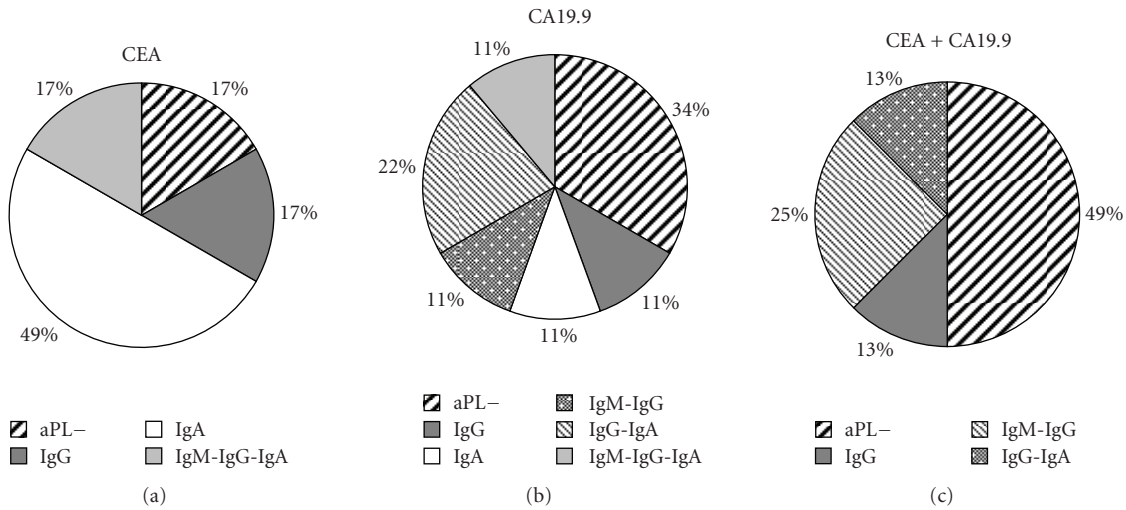

Figure 3: Antiphospholipid antibodies in tumor marker positive patients. The data are expressed as the percentage of IgM, IgG, and IgA anticardiolipin (aCL) positive and of aCL negative in relation to (a) CEA, (b) CA19.9, (c) and CEA+CA19.9.

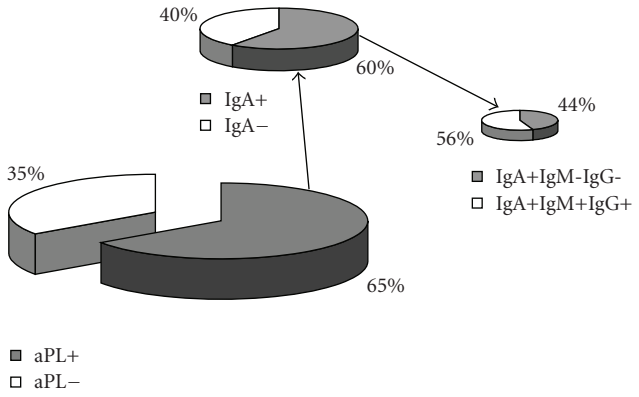

Figure 4: Anticardiolipin (CL) positive and negative patients. The data are expressed (a) as percentage of aCL− and aCL+, (b) as percentage of IgA- and IgA+ among aCL+ patients, and (c) as percentage of IgA+IgM-IgG- and IgA+IgM+IgG+ among IgA+aCL patients.

4. Discussion

It is known that the production of secretory IgA alone can prevent infection by invasive enteric pathogens [22] and that there exists a relation between this secretion and the motility in human proximal small intestine [23]. In a variant of Henoch-Schonlein purpura, characterized by abdominal pain, vomiting, hematemesis, and endoscopic multiple lesions, there is an IgA deposit along the plasma membranes of the enteric endothelial cells [24]. These data clearly indicate the importance of IgA in gastroenteric system. Recently it has been demonstrated that all the three isotypes (IgM, IgG, and IgA) of the aCL are able to induce the thrombus formation in vivo, [25]. Staub et al. have reported that even if a pathogenic role for IgA anti-β2GPI antibodies in atherosclerosis is yet to be confirmed, IgA anti-β2GPI response in patients with acute cerebral and myocardial syndromes may represent one of the links between autoimmunity and atheromatosis [26]. Nowadays, there are more observations regarding the involvement of IgM and IgG aCL in tumor disease with high risk to develop thrombotic complications [19, 27, 28]. Miesbach et al. [29] have reported as frequently catastrophic antiphospholipid syndrome (*CAPS*), characterized by the rapid chronological development of fulminant thrombotic complications, occurs in patients with underlying malignancies. However, until now no existing data regarding the role of IgA aCL in patients with tumor are found. In this study, we show for the first time the association between IgA aCL and gastroenteric tumors. The patient at the first observation for gastroenteric tumors with CEA, CA19.9, and CEA+CA19.9 positive has moderate or high value of aCL antibodies in high percentage. Our data support precedent observations indicating that the patients affected with gastroenteric tumor are at high risk to develop thrombotic complications. Moreover, a high prevalence of aCL antibodies is not detected only by the IgM and IgG aCL standard test but also by IgA aCL test. In fact there are patients with IgA- aCL positive and IgM-IgG-aCL negative. Therefore, testing only IgM-IgG-aCL, you miss 4 patients with tumor aCL positive that could have thrombotic complications. It is important to know that of 6 patients, that are only CEA positive, 3 are only IgA-aCL positive. In conclusion, we propose to include in the patients with gastroenteric tumor the evaluation of IgA-aCl together to IgM-IgG-aCL test to better prevent eventual thrombotic complications.

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