Monoclonal gammopathy of unknown significance in pregnancy

A. Chryssikopoulos¹, M.D., A. L. Dalamaga², M.D., D. Hassiakos³, M.D.

¹Second Department of Obstetrics and Gynecology; ²Med. School, Univ. of Athens & The Hematological Center
“Areteion” Hospital, Athens (Greece)

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Introduction

Monoclonal gammopathy of unknown significance (MGUS) belongs to the plasmocytic displasias and is characterized by an uncontrolled increase of the plasmocytes as well as the synthesis and secretion of homogeneous γ-globulin (M-Component) with absence of clinical findings. Although there have been cases of MGUS associated with a great number of non-malignant and malignant conditions [1], as far as we know no such case has been reported in association with pregnancy.

Case Report

A 33-year old female who was randomly examined in 1990 was found to have a significantly increased monoclonal fraction of immunoglobulin IgA, while both the serum levels of the immunoglobulins IgG and IgM and the C₁ complement factor were lower than those of the normal subjects (Table). The myelogram showed an increase in plasmocytes of 10%. Clinical and laboratory controls were normal. A diagnosis of MGUS was made and the patient was placed under clinical and laboratory checks at regular intervals without any change of findings.

In 1993 the patient, after two years of marriage, presented at our clinic with primary sterility. Complete work-up including spermodiagram and laparoscopy revealed anovulation as the causative agent. Treatment with clomiphene citrate for four months, gonadotropins for eight months, despite successful induction of ovulation, did not conclude in pregnancy. The patient finally conceived with IVF-ET after trying for two months. The pregnancy developed normally and on the 39th week the patient delivered by cesarean section a healthy female weighing 3,850 gr.

Immunoglobins IgG, IgA, IgM and C₁ and C₂ complement factors were determined during the 1st, 2nd and 3rd trimester of pregnancy, delivery, and puerperium in the mother as well as in the umbilical cord of the neonate. Moreover, both the immunoglobulins and the complement factors were determined 4 1/2 months after delivery in the mother’s and neonate’s serum. Determinations were done by the Turbitime system (Behring Turbitime System). The results were compared with those of a great number of controls at our clinic (Table).

Results and Comment

The following are included in plasma-cell and immunocell dyscrasias: 1) multiple myeloma, 2) Waldenström’s macroglobulinemia, 3) heavy chain disease, 4) amyloidosis and, 5) benign monoclonal gammopathy in which an increase of plasmocytes in the bone marrow and the existence of monoclonal γ-globulin fraction (paraprotein fraction) without the presence of other pathological findings are observed [1].

The incidence of MGUS is 1% in subjects more than 25 years of age [2] and the appearance of the disease increases with age. In subjects over 70 years of age MGUS occurs in 5%, over 80 years in 10% and over 90 years in 20% [2], while in young subjects it appears very rarely (0.1%-0.3%). The increased level of monoclonal protein may remain stable for a long period of time while 5% of young subjects present with malignant plasmocytic dyscrasia in the course of time [3].

The exact cause of MGUS remains unexplained. Osterland [4] maintains that MGUS constitutes a premalignant state. Since several M-components have a specific antibody activity [2], it has been supposed that MGUS may constitute a monoclonal response in the antigens of infections, cancerous factors or other forms of immunological stimulations. On the other hand, hereditary factors are considered responsible for the presence of MGUS [1] while at the same time the view has been sustained that MGUS is related to the failure of the T-lymphocyte functions which is observed in the course of age [2].

Our patient, who was incompatible to pregnancy for four years, preserved a picture of increased serum levels of IgA (about 14 times), with a concomitant decrease of IgG, IgM levels and the C₁ complement factor for 12 months with ovulation inducers and a 2-month IVF-ET program (1.7, 2.8 and 1.7 times, correspondingly).

During pregnancy the serum level of the pathological monoclonal fraction of IgA (M-component) increased in the 1st trimester of pregnancy, fell significantly in the 2nd trimester, with a de novo increase in the 3rd trimester and maintenance of high levels at delivery and puerperium. The postpartum (4 1/2 months) IgA serum level approached the pre-pregnancy values. The IgG, IgM serum levels and the C₁ complement factor decreased, though were higher than corresponding levels in normal subjects during pregnancy, as can be deducted from the controls (Table). In spite of that, the immunological singularity of pregnancy did not actually affect the correlations existing before. In the neonate during delivery (umbilical cord) the serum levels of immunoglobulins...
Table — Immunoglobulin serum levels and C₄, C₃ complement factors (mg/dl, mean±SD) in the controls, in the patient before and during pregnancy, delivery, and puérperium, as well as in the umbilical cord on the neonate

<table>
<thead>
<tr>
<th></th>
<th>Before pregnancy</th>
<th>1st trimester of pregnancy</th>
<th>2nd trimester of pregnancy</th>
<th>3rd trimester of pregnancy</th>
<th>Delivery (n=18)</th>
<th>Puérperum (n=18)</th>
<th>Umbilical cord (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (n=34)</td>
<td>Pat.</td>
<td>Control (n=55)</td>
<td>Pat.</td>
<td>Pat.</td>
<td>Control (n=18)</td>
<td>Pat.</td>
</tr>
<tr>
<td>IgG</td>
<td>1303±251</td>
<td>771±20</td>
<td>983±172</td>
<td>548</td>
<td>867±196</td>
<td>501</td>
<td>939±162</td>
</tr>
<tr>
<td>IgA</td>
<td>206±64</td>
<td>2880±120</td>
<td>140±33</td>
<td>3400</td>
<td>132±31</td>
<td>909</td>
<td>142±25</td>
</tr>
<tr>
<td>IgM</td>
<td>173±51</td>
<td>62±9</td>
<td>141±30</td>
<td>37</td>
<td>137±23</td>
<td>57</td>
<td>144±69</td>
</tr>
<tr>
<td>C₄</td>
<td>124±30</td>
<td>73±8</td>
<td>138±34</td>
<td>100</td>
<td>164±35</td>
<td>132</td>
<td>166±31</td>
</tr>
<tr>
<td>C₃</td>
<td>31±9</td>
<td>30±2</td>
<td>35±9</td>
<td>12</td>
<td>32±7</td>
<td>61</td>
<td>35±9</td>
</tr>
</tbody>
</table>

* 4 1/2 months after delivery

IgA and IgM were totally normal and the serum levels of IgG and C₄ complement factor had decreased, which of course returned to normal levels during re-examination 4 1/2 months. The immunological status of the neonate does not advocate the view which incriminates hereditary factors in the manifestation of the disease [1]. On the contrary, Tissot et al. [5] have reported a case of a 30-week old premature infant with MGUS who possibly inherited the disease from his mother.

As far as we know, there are no studies which report that MGUS can influence fertility negatively. In spite of that, failure of conception after a 12-month successful ovulation induction, and the speedy successful conception with IVF-ET raises the suspicion that the characteristic increase in MGUS serum level of immunoglobulin IgA may influence the in vivo conception negatively as in the case of the tubes. Oviductal fluid appears to be derived from a combination of selected transudation from the blood as well as active secretion from its hormonally influenced epithelial tissues [6]. The concentrations of immunoglobulins IgG and IgA within the oviductal fluid is approximately one-tenth the concentration in the serum [7, 8]. The levels of both immunoglobulins decrease to extremely low levels around the time of ovulation, probably due to estrogens, followed by an increase within 3-5 days after ovulation [8]. The above show that both fertilization as well as early embryo development occur in the environment of the oviductal fluid containing very low levels of immunoglobulins. In our case the IgA plasma levels, during the period treated for sterility, were 13-15 times higher (table) and apparently higher in the tubal fluid as well. Since the oviductal fluid contains extremely low levels of immunoglobulin IgA, in physiological conditions, such as the time of ovulation, the higher levels seen in our patient could very well have had detrimental effects both on the fertilization as well as the early embryo development; this was avoided in our case with the use of the method of IVF-ET.

Despite the rarity of cases of MGUS in young subjects, a more detailed study in this direction would be interesting.

In conclusion, the administration of ovulation inducers and pregnancy and puérperium in this patient with MGUS did not affect the correlations of the immunoglobulins existing in the mother before pregnancy while in the neonate they were totally normal.

References


Address reprint requests to:

ATHANASIS CHRYSSIKOPOULOS
Second Dept of Obst. & Gynecol.
Med. School, University of Athens
Arteion Hospital
76 Vas. Sophias Ave.
Gr-11528 Athens (Greece)