Etiology and Pathogenesis

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Since the first definition of IGM in 1971 by Kessler and Wolloch, this entity's etiology and pathogenesis have not been exactly explained yet.

Various reasons such as α1-antitrypsin deficiency; oral contraceptives; gestation, birth, and breastfeeding; hyperprolactinemia; smoking; microbial agents; ethnicity; and autoimmunity have been suggested, but have not yet been fully proved up to now [1, 2].

1 α1-Antitrypsin Deficiency

In a 37-year-old female patient diagnosed with IGM, alpha-1 antitrypsin deficiency was found on investigation. This, the first concurrent alpha-1 antitrypsin deficiency and IGM were reported [3]. However, no other publication other than this case report has been found in English literature. This association is most likely due to a coincidence.

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2 Oral Contraceptives

It has been suggested that oral contraceptives may play a role in the pathogenesis of IGM and this has been thought to occur as a consequence of increasing breast secretion. However, the frequency of oral contraceptive use in patients with IGM is variable (0–40%). Although it does not seem to have a direct effect, it may have a possible contribution to the pathogenesis of IGM through hormonal changes [4–9]).

3 Hyperprolactinemia

In the etiology and pathogenesis of IGM, drug-induced hyperprolactinemia and prolactinomas have been another interesting topics [10–15]. In an article from China (only the "abstract" can be obtained), high serum prolactin level was determined in 39.7% of 300 patients with granulomatous lobular mastitis [16].

Li and McGregor [14] reported a case of IGM associated with hyperprolactinemia. Their patient did not respond to antibiotic treatment; however, they did respond to bromocriptine that is used for hyperprolactinemia. Destek et al. [12] reported that their patient with IGM who did not respond to antibiotic (10 days) and steroid treatment (2 months) and then a pituitary prolactinoma was diagnosed. Cabergoline, a prolactin inhibitor, was administered for hyperprolactinemia. It was observed that IGM resolved in the fourth month of cabergoline treatment. In another case report, an IGM patient associated with risperidone-induced hyperprolactinemia is presented. The patient's risperidone treatment was changed to quetiapine and the patient's lesions resolved with steroid treatment [13].

The following questions, "Does hyperprolactinemia really play a role in IGM etiology and pathogenesis?" or "Is this union a coincidence?," should also be answered. In patients with hyperprolactinemia, most common manifestations are menstrual disturbances, weight gain, galactorrhea, headache, visual field defects, and infertility [17]. In our previous study [8], there was no symptom or sign suggestive of hyperprolactinemia. Additionally, we found that the time since the last birth ranged from 1 month to 37 years (median, 4 years) in IGM patients. When the time of IGM patients' last birth were grouped, IGM was observed after 24 months at most.

There is no such information mentioned about the number of breastfeeding patients with high prolactin levels in the article by Chen et al. [16]. Especially if the number of breastfeeding women is high, this may explain the number of women with high prolactin levels. However, all these findings are not sufficient to exactly explain the role of hyperprolactinemia in the etiology and pathogenesis of IGM.

4 Gestation, Birth, and Breastfeeding

Although IGM can be seen in both men and women at any age, it is usually seen in women who are premenopausal, are parous, and have a breastfeeding history (Fig. 1) [8, 18]. As seen in Fig. 1, the majority of IGM patients are in the reproductive age range.

Idiopathic granulomatous mastitis can be seen in women who have never been pregnant or have not given birth [10, 19, 20]. In our series, the percentage of nulliparous women was 4.5% [8].

The question "Is pregnancy an etiological factor of IGM?" does not have an exact answer. The percentage of pregnant patients with IGM at diagnosis was 4.5% [8]. However, there may be a triggering factor [21]. Sener Bahce and Aktas [22] reviewed 35 IGM patients. They reported that four of six patients with erythema nodosum and arthritis were pregnant at the time of IGM diagnosis.

In addition, the percentage of pregnant and breastfeeding patients at IGM diagnosis were 4.5% and 3.7%, respectively [8]. While these rates may give a doubtful impression about the role of pregnancy in the etiopathogenesis of IGM, it shows that extramammarian findings such as erythema nodosum and/or arthritis are more common in pregnant women [22–26].

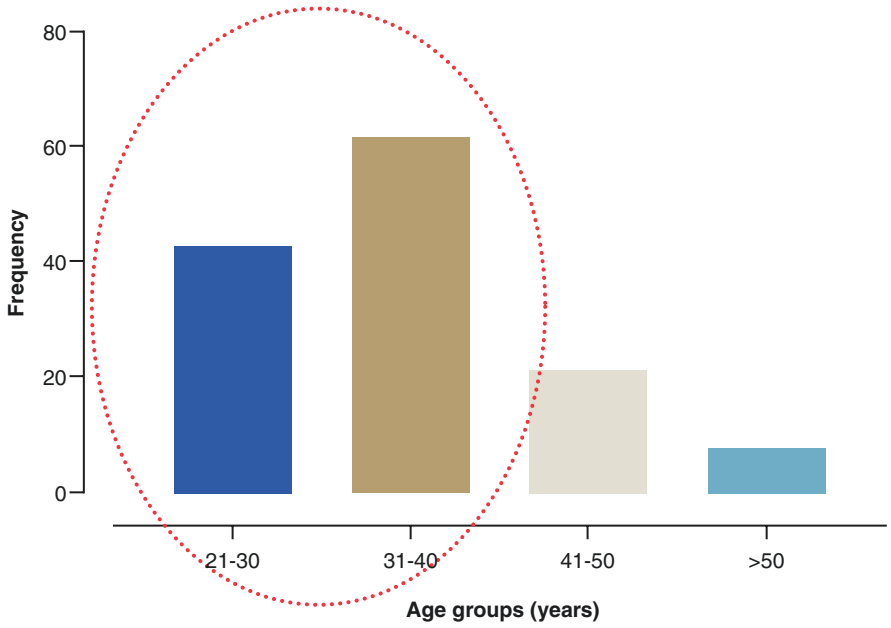

Fig. 1 Age distribution of our IGM patients

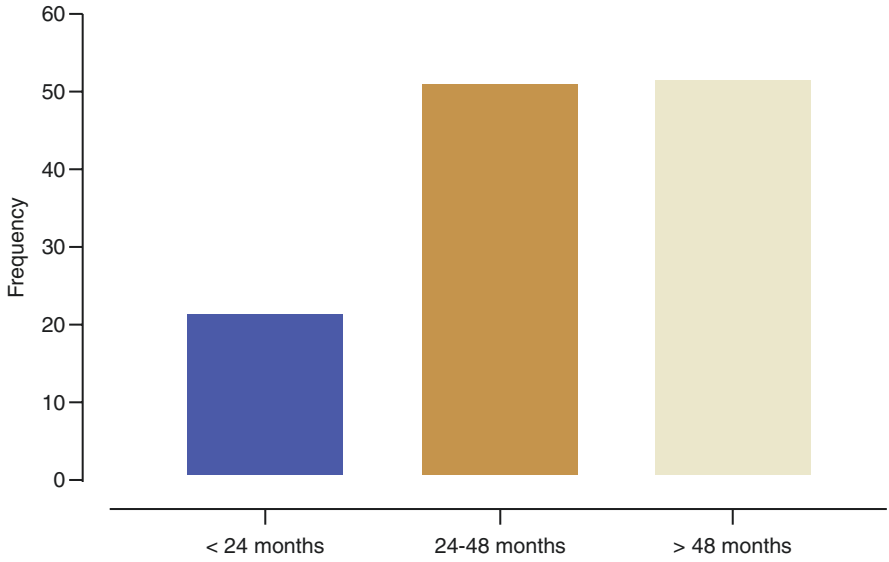

Fig. 2 Duration between the diagnosis and last birth in our IGM patients

Another factor in the etiology of IGM is breastfeeding at the time of diagnosis [1, 2]. There are two important points in breastfeeding: the breastfeeding history of the IGM patient and whether breastfeeding is present at the time of the diagnosis or not. Patients with IGM diagnosis before the reproductive age and, although rare, the fact that men may be diagnosed with IGM suggest that breastfeeding at the time of diagnosis has no direct role in IGM etiology [5, 18].

In our study [8], the time from the last childbirth to the diagnosis of IGM was investigated. The time periods were divided into three groups: <24 months, 24–48 months, and > 48 months. Approximately three quarters of patients were found to be diagnosed 24 months after the last delivery (Fig. 2).

As emphasized in the article, this brings highlight to the question: "Does breastfeeding prevent or delay the development of IGM, suggesting the possible contribution of autoimmunity/immune dysregulation?"

5 Autoimmunity and Immune Dysregulation

Recently, autoimmunity and immune dysregulation has been emphasized in the etiology of IGM. The arguments made are the use of immunosuppressive drugs such as corticosteroids and methotrexate in the treatment of IGM, the presence of common symptoms observed in rheumatological diseases such as erythema nodosum or arthritis, and coincidence with some rheumatological diseases such as Sjogren's syndrome and systemic lupus erythematosus [8, 27–33].

One of the first studies on this subject was by Erhan et al. [34]. The authors completed an immunohistochemical investigation of T and B lymphocytes in the specimen. A predominance of T cells was observed. In a similar study by Chen et al. [16], CD3-positive lymphocytes in the peripheral aggregation zone of neutrophils within granulomatous lesions were seen more than CD20-positive lymphocytes. In light of these findings, we compared the peripheral lymphocyte subgroups of IGM patients to investigate whether the change in T and B lymphocytes had a reflection in the peripheral blood [35]. We found that while IGM patients' T helper lymphocytes were lower than the control group, cytotoxic T lymphocytes and natural killer T cells were higher. All these findings may propound a possible immune dysregulation in IGM [36].

There are two cytokine studies in IGM [37, 38]. In our study, we found that levels of the interleukin-8, interleukin-10, and interleukin-17 were higher in patients with IGM than controls. We thought that interleukin-8 and interleukin-17, known as proinflammatory cytokines, had a role in the pathogenesis of IGM. High interleukin-10 levels especially in patients in remission reduced the release of proinflammatory cytokines as well as suppressed their function to control the inflammation in IGM [37]. Saydam et al. [38] found that levels of interleukin-22 and interleukin-33 were higher in IGM patients and concluded that these findings support the role of autoimmunity in the etiopathogenesis of IGM.

Autoantibodies have also been studied in patients with IGM. Ozel et al. [39] detected the rheumatoid factor in six of eight IGM patients, antinuclear antibody in two patients, and anti-double-stranded DNA positivity in two patients. In another study, they investigated antinuclear antibody and extractable nuclear antigen in patients with IGM [40]. However, they emphasized that their study did not support the autoimmune basis for IGM. In our study [41], we investigated the rheumatoid factor, antinuclear antibody, anti-double-stranded DNA antibody, anti-cyclic citrullinated peptide antibody, and perinuclear antineutrophil cytoplasmic antibody in IGM patients with active lesions, in remission, and in the control group. But our study did not support a positive clinical outcome of these autoantibodies in IGM.

An interesting finding is the seasonal fluctuations of IGM as highlighted in the epidemiology section [8, 42]. The fact that IGM is common especially in the spring and early days of summer brings to mind the question of whether IGM is an autoimmune disease triggered by viral infections.

In conclusion, all these findings suggest that immune dysregulation and autoimmunity play an important role in the etiopathogenesis of IGM.

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