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(CASE REPORT)

A case report of nonepisodic angioedema with eosinophilia in a young Japanese female followed up with serum cytokines and immunoglobulins

Masaaki Minami [1,*] and Takefumi Suzuki [2]

[1] *Department of Bacteriology, Nagoya City University, Graduate School of Medical sciences, Nagoya, Japan.*
[2] *Suzuki Clinic, Nishio, Japan.*

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Abstract

NEAE (Nonepisodic angioedema associated with eosinophilia) is a relatively common allergic disease in East Asia in which angioedema is confined to the extremities, is transient and does not recur, and is not accompanied by fever or highly elevated IgM. In this study, we report a case of NEAE disease with edema of the extremities in a young female who was able to be followed up with serum cytokines and serum immunoglobulins as biomarkers. Our results suggest that not only clinical findings but also serum biomarkers are useful in monitoring the disease status of NEAE.

Keywords: NEAE; Biomarker; Cytokine; Immunoglobulin

1. Introduction

Episodic angioedema with eosinophilia (EAE) is a syndrome characterized by recurrent episodes of angioedema, fever, leukocytosis, eosinophilia, elevated serum IgM, increased body weight, and a benign clinical course lacking any internal organ involvement. Geich et al originally described it in 1984 [1]. More than 40 cases with symptomatic presentations and laboratory findings like EAE have reported, but these cases have not involved recurrent attacks. Thus, those cases have subsequently designated as nonepisodic angioedema with eosinophilia (NEAE) [2]. In this paper, we described patients whose clinical and laboratory features were similar to those observed in previous case of NEAE and able to observe the pathology with serum cytokines and serum immunoglobulins as biomarkers.

2. Case Presentation

25-year-old women presented with edema of her hand and low legs in September. The edema was distributed symmetrically on both patient's upper and lower extremities and pitted. She had apruritic rash on her low legs. Her shoes size was increasing from 24 to 26. She had also experienced mild joint pain in both knees and fingers. She had also urticaria in her breast. Her body weight had increased by 10 kg over those 4 weeks. This was her first episode of the reported symptoms. Her family and past medical histories and family histories, including any allergic diseases, were unremarkable.

Laboratory tests revealed leukocytosis (12300/mm^3) with eosinophils in the peripheral blood. The eosinophil count was 6519/mm^3. Serum IgE had increased to 40 IU/mL, but IgA, IgG and IgM levels were all within normal limits. Although antinuclear antibody was positive (160 times), no other clinical findings were suggestive of autoimmune disease or parasite infestation. No abnormal findings were observed in the serum chemistry that would be reflective of renal or hepatic dysfunction.

* Corresponding author: Masaaki Minami
Department of Bacteriology, Nagoya City University, Graduate School of Medical sciences, Nagoya, Japan.

Thus, we speculated the patient with NEAE. Since no exacerbation of symptoms was observed, the patient was placed under observation. The edema and rash began to evidence improvements in October. The knee and finger arthralgia also clearly improved. The eosinophil count decreased to 1106 /mm^3 after four weeks and to 597 /mm^3 after eight weeks. The patient was free of symptoms at four months.

We obtained consent from the patients and collected blood for 3 days between October and December and examined the biomarkers in the serum. Immunoglobulins (IgG, IgA, IgM, anti ss-DNA IgG, and anti-ds-DNA IgG) and IL-5 were measured by LSI Medience Co. (Tokyo, Japan), and cytokines (TNF-α, IL-1β, IL-17, and PGE2) were measured by ELISA kit (R&D Systems, Inc.: MN, USA). As a result, immunoglobulins and inflammatory cytokines showed a decreasing trend as the days passed (Figure 1-3). IgM and anti ss-DNA IgG were higher than normal. However, anti-ds-DNA IgG and IL-5 were below the limit of measurement and could not be compared.

We followed the patient for six months and observed no recurrence of either the symptoms or the eosinophilia.

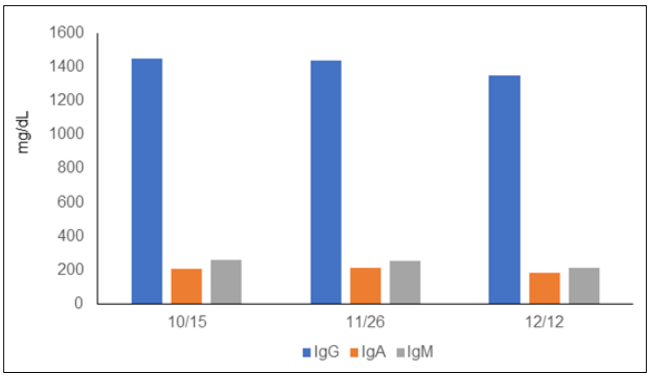

Figure 1 The change of IgA, IgA, IgM values

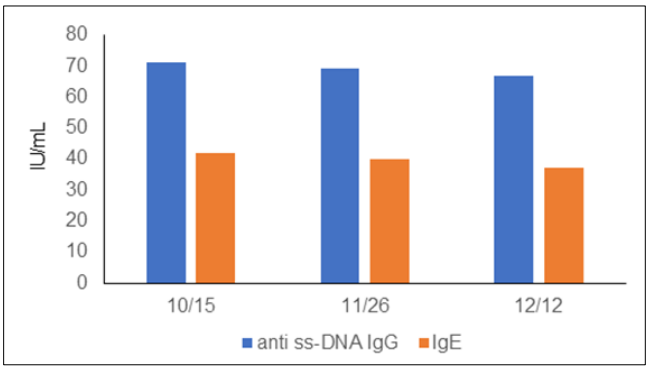

Figure 2 The change of anti ss-DNA IgG, IgE values

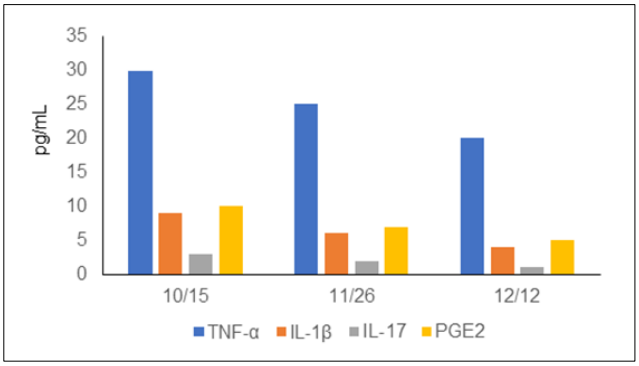

Figure 3 The change of TNF-α, IL-1β, IL-17, PGE2 values

3. Discussion

In NEAE, the angioedema is normally localized to the hands and the proximal portion of the lower legs, whereas in EAE the angioedema frequently extends farther down the extremities including the face [3]. The edema in EAE is attended by a substantial increase in body weight [3]. Urticarial is also present in about 30% of patients [2]. More than 40% of NEAE patients from Japan have arthralgia [4]. Symptoms have been reported to improve in 6 to 9 weeks, and our results also agree with this [5].

We did not administer any therapeutic agents and followed the patient, but there are reports of rapid improvement with low dose prednisolone (15 mg/day) as a treatment for NEAE, which is one of the definitions of the disease [2][6][7]. This is one of the definitions of the disease [2]. However, there are also reports of cases other than our case that improved without treatment, so the treatment method needs to be investigated by accumulating more cases in the future [8].

The pathogenesis of NEAE has not been clarified. The cause of the sudden increase of eosinophil remains unknown, as with idiopathic hyper eosinophilic syndrome. Activated T helper type 2 (Th2)-cell-derived cytokines, mainly IL-5, were involved in the migration and activation of eosinophil in the skin. T cell produces an excess of IL-5 [9]. Another report showed that IL-5 levels were determined to be a lower, and TNF-α levels were higher in the acute phase of NEAE than in the acute phase of EAE [10]. Previous studies have also reported that TARC/CCL17 serum levels are elevated in NEAE [11]. IL-5, VEGF-A, RANTES/CCL-5, Eotaxin-1/CCL11, MCP-4/CCL-13, TARC/CCL-17, and Eotaxin-3/CCL-26 showed a downward trend with improvement in disease status [12]. Furthermore, TNF-α, IL-5, TARC, MCP-4, Eotaxin-1, and Eotaxin-3 showed significant correlation with edema index [12]. Although we do not show the results of examining all these biomarkers, we agree at least for TNF-α and IL-5. As RANTES and Eotaxin-1 were induced by TNF-α, Changes in these biomarkers may have been seen in our case as well [12].

We present the limitations of this study. We have not been able to collect serum samples during the acute phase of the disease, so we have not been able to follow up the complete biomarkers such as cytokines. However, the results for cytokines in the improvement phase are consistent with previous reports and show useful results for NEAE.

4. Conclusion

In this work, we have described the case of a Japanese patient with NEAE. The majority of these NEAE cases have been reported in Eastern populations, especially Japanese. This ethnic or regional distribution may be an important characteristic of NEAE. It suggested that NEAE may have a racial predisposition toward Asian population. In the future, more detailed large-scale studies, including genetic analysis, are desired.

Compliance with ethical standards

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Disclosure of conflict of interest

All authors declare no conflict of interest of regarding the publication of this paper.

Statement of informed consent

Informed consent was obtained from individual participant included in this study.

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