

Histological and immunohistological study of late-onset reactions to gold sodium thiosulfate

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Twenty-two allergens including gold sodium thiosulfate (GST) of the TRUE Test were approved as the Patch Test Panel (Sato Pharmaceutical, Tokyo, Japan) in Japan in 2015. The current Japanese baseline series consists of that panel and two other allergens since 2015.¹ After this series was available, many cases of late-onset positive reactions to GST were reported.² We encountered two such cases that we studied histologically and immunohistologically.

CASE REPORTS

Case 1 A 29-year-old woman was patch tested with Japanese baseline series in 2015. Past medical history included urticarial vasculitis. The patient had dental metal implants, and she had her earlobes pierced 10 years earlier (Table S1). We recorded positive reactions to nickel sulfate and thiomersal and negative ones to others, including gold sodium thiosulfate (GST) on day (D) 7. Because the patient developed a pruritic rash 44 days after application, she presented to the dermatology department the next day. Physical examination revealed rectangle-shaped edematous erythema with vesicles at the site where GST had been applied. We biopsied this reaction that same day. Histopathological findings demonstrated perifollicular infiltrate of lymphoid cells in the upper and middle dermis (Figure 1A). Liquefaction was noted in the epidermis and outer root sheath (Figure 1A). The phenotype of lymphoid cells showed that most were characterized by CD3+ cells, and CD20+ cells were mingled. Among the former, the number of CD4+ cells were significantly more frequent than CD8+ ones (Figure 2A,B). CD1a+ cells were observed in the epidermis (Figure 2C) and CD68+ cells in upper dermis.

Case 2 A 23-year-old woman was patch tested as above for screening. Past medical history included inflammatory bowel disease. The patient received dental metal implants when about 10

years old, and was treated by an orthodontist 7 years before consultation (Table S1). She never had her body pierced (Table S1). While all applied allergens were negative at D2, D3, and D7, she developed a pruritic rash 1 month after application. Because that rash had not disappeared, she presented at the dermatology department 79 days after application. Physical examination revealed a dark reddish, infiltrated erythema with scattered papules at the site where GST had been applied. This was biopsied on the same day. Histopathological findings demonstrated dense infiltrate of lymphoid cells in the upper and middle dermis, in particular, perifollicular regions, respectively (Figure 1B). These cells included atypical lymphocytes and cells with nuclear fission (Figure 1C). The phenotype of lymphoid cells showed that CD3+ cells infiltrated, and CD20+ and CD79a+ B cells were interposed. There was no significant difference between the number of CD4+ and CD8+ cells (Figure 2D,E), and there were many CD1a+ cells in the epidermis (Figure 2F) and CD68+ cells in the dermis.

DISCUSSION

Although a late-onset reaction to gold is not rare, its mechanism is controversial.³⁻⁷ One hypothesis is sensitization to gold due to patch testing, especially if such patients sometimes positively reacted to gold at D3 on a second patch testing.² Another notion is that patch test reactions to gold may be affected by serum gold level.⁸

Möller et al described histological and immunohistological findings of long-lasting patch test reactions to gold: Those were characterized by intense dermal infiltrate of CD4+ and CD8+ cells.⁹ In addition, they analyzed flare-up reactions to gold and suggested that antigen-presenting cells may be instrumental in such reactions.^{10,11}

We compared the histopathological and immunohistological findings of these cases. At first, the difference between two cases

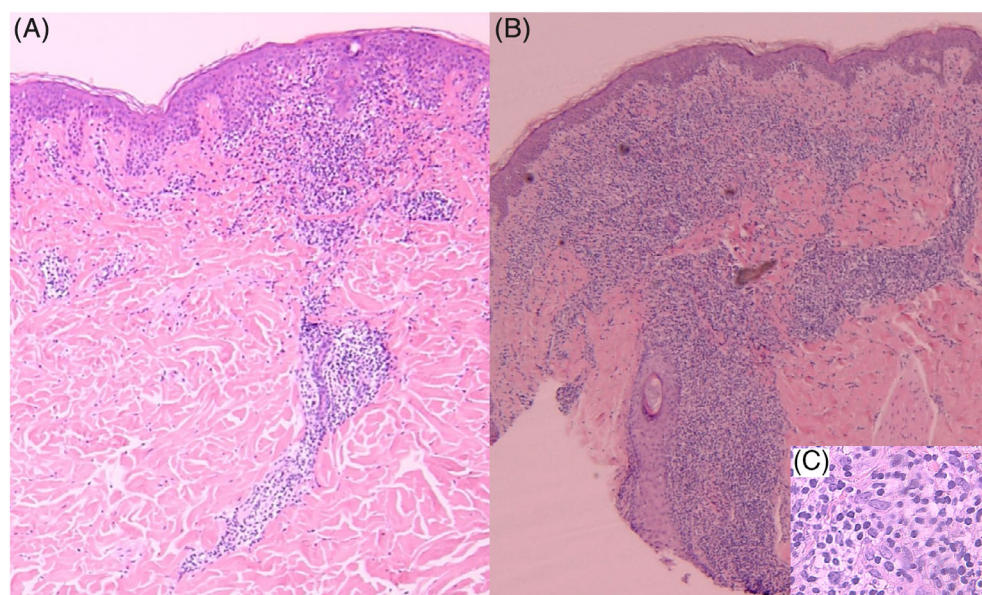


FIGURE 1 Comparison of histopathological findings between cases 1 and 2. (A) case 1, lower magnification. (B) case 2, lower magnification. (C) case 2, higher magnification

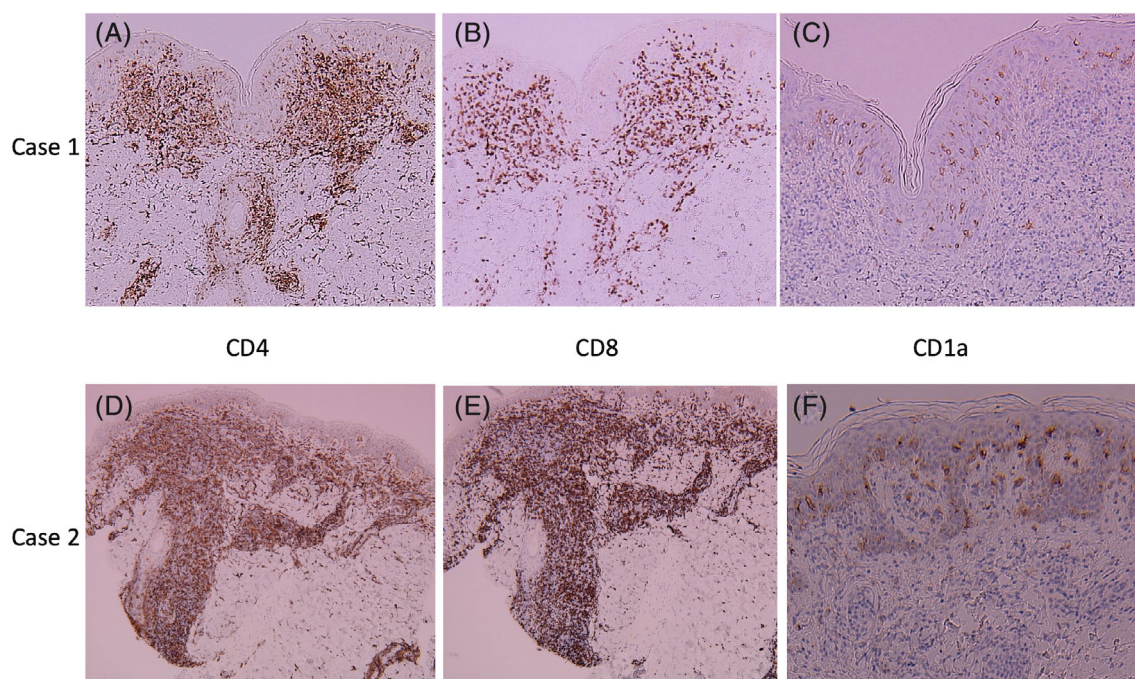


FIGURE 2 Comparison of phenotype (CD4, CD8, and CD1a) between cases 1 and 2

was spread of inflammation: limited in the upper dermis and perifollicular regions in case 1, and reaching into the deeper dermis in case 2. Second, composition of the cellular infiltrate was different: CD4+ cells mainly in case 1, and various ones in case 2. Persistent nodules on ear piercing sites are the most frequent feature of allergic contact dermatitis to gold.^{12,13} Histopathological findings of the nodules were dense infiltration in dermis, and some cases showed pseudolymphoma-like reactions.¹²⁻¹⁵ Therefore, various cells including atypical lymphoid cells should be regarded as allergic reactions to gold.

Metal allergy is not an allergic reaction to a metal itself but to an ionized metal.¹⁶ Gold is known as a metal whose potentials of electrode reactions are high and which has the lowest ionization tendency among metals.¹⁷ To develop contact dermatitis, causative agents including metals have to be absorbed. In this process, hair follicles play an important role not only for the penetration of chemicals, but also as a reservoir of penetrating substances.¹⁸ We speculate two possibilities for late-onset reactions to GST. One is that ionized gold might take longer than other metals for penetration in some gold-sensitive individuals. Another is that gold ions could be hardly recognized by

immune system. This is based on findings of case 1: Inflammation is present at limited sites in and around hair follicles, despite 44 days post application. Findings of case 2 suggested that absorbed gold ions left hair follicles and diffused to the surrounding spaces. Bruze et al suggested a third possibility, namely, that the general anti-inflammatory properties of gold salts might influence such late-onset reactions.¹⁹ Positive reactions to gold last a long time. This suggests that ionized gold was still present, and allergic reactions to it were persistent in such cases. Immunohistological findings of case 2 confirmed this, since more Langerhans cells were observed and their morphology was more activated than in case 1. Pita da Veiga et al described Langerhans cell hyperplasia at late and persistent reaction to GST.²⁰ Bruze et al suggested that long duration may be explained by a tendency to initiate chronic inflammation.¹⁹

In conclusion, we speculate that late reaction to GST may be due to the specific characteristics of gold ions in terms of penetration into skin and/or being recognized by the immune system. In addition, long-persistent positive reactions to gold might be due to the presence of diffused gold ions, which are eliminated only slowly.

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AUTHOR CONTRIBUTIONS

Yuriko Iwahashi: Writing-original draft. **Hanako Takei:** Methodology. **Yurina Kasa:** Formal analysis. **Hirokazu Uno:** Data curation. **Shinpei Ohtoshi:** Data curation. **Tokio Nakada:** Supervision.

CONFLICT OF INTERESTS

The authors declare no potential conflict of interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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Table 1. Comparison of clinical findings between case 1 and 2.

	Case 1	Case 2
Age, Gender	29Y, F	23Y, F
Dental metal	+	- (+ when infant)
Ear piercing	+	-
Onset of positive reaction	79 days post application	1 month post application
Period between onset and removal	1 day	7 weeks