48, XXYY Syndrome Associated with Ethylenediaminetetraacetic Acid (EDTA)-dependent Pseudothrombocytopenia

Takahito Kodama, Hirokazu Imai, Yasushi Nakamoto, Tamotsu Sugawara* and Akira B Miura

A 56-yr-old man with hypogonadism, gynecomastia, and mental retardation was evaluated for chromosome constitution and thrombocytopenia. Chromosomal analysis demonstrated the mosaicism of 48, XXYY and 47, XXY in the peripheral lymphocytes. Twenty out of twenty-five cells were 48, XXYY karyotype and the remaining five were 47, XXY karyotype. Thrombocytopenia was the EDTA-dependent pseudothrombocytopenia type 1 (platelet agglutination). Serological examination suggests that the platelet agglutinin belongs to IgM-kappa type. The present case exhibited both EDTA-dependent pseudothrombocytopenia and the 48, XXYY syndrome. Although this combination may have occurred purely by chance, the possibility of whether or not the mosaicism of lymphocytes produces platelet agglutinin remains to be clarified.

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Introduction

The 48, XXYY syndrome was first described by Mudal and Ockey (1) in 1960 as a “double male,” and placed in the category of Klinefelter’s syndrome, along with 47, XXY chromosome. However, several investigators (2, 3) have emphasized that the 48, XXYY syndrome should be classified as a separate entity since there are physical, dermatographic, and mental differences from Klinefelter’s syndrome. The question of the genetic origin of the extra chromosomes has not been resolved.

Pseudothrombocytopenia is platelet clumping in the presence of anticoagulant (ethylenediaminetetraacetic acid, EDTA) resulting in a spuriously decreased platelet count. EDTA-dependent pseudothrombocytopenia is known to exist in two forms: type 1-platelet clumping (agglutinin, not aggregation), and type 2-platelet adhesion to polymorphonuclear leucocytes (platelet satellitism). These are associated with malignancies (4, 5), acute and chronic liver disease (6, 7), autoimmune situations (4, 8, 9), and chronic glomerulonephritis (10). Platelet agglutinin has been suggested as being made of immunoglobulins.

In this study, we report on a rare case of the 48, XXYY syndrome (47 XXY/48 XXYY mosaicism) associated with EDTA-dependent pseudothrombocytopenia.

Case Report

A 56-yr-old Japanese man was admitted to Akita University Hospital because of thrombocytopenia on January 13, 1988. Regarding his history, his mother had had a full-term pregnancy, and delivery had been normal. According to his sister, he had behavioral problems at school. Reliable medical and personal histories were not kept, because his I.Q. was 60 (Suzuki and Binet’s scale). He was married at age 18. At the age of 30, he began to work for a newspaper and milk delivery service. He did not show aggressive behavior. At 35 yr of age, he underwent operations for ileus, and bilateral mastectomy for gynecomastia. At 38 yr of age, appendectomy was performed at a local hospital. Since the age of 50, he has been followed up for abdominal discomfort in the outpatient clinic of Honma hospital. One month before admission to Akita University Hospital, he complained of abdominal pain, and was diagnosed as having thrombocytopenia.

The temperature was 36°C, pulse rate was 78/min, and respiration was 26/min. The blood pressure was 120/60mmHg. His ht was 162cm and wt, 68 kg. His voice was high-pitched like a woman. The third and fifth...
interphalangeal bones of right hand were shorter than normal. The chest was funnel-shaped, and operation scars were visible in the breast area. The abdomen was protuberant without organomegaly. There were operation scars from the ileus and appendectomy. No signs of teleangectasia were found. Axillary and pubic hairs were sparse. The testicles were as small as the tip of an index finger, and soft. Penis was 3 cm in length. There was an operation scar in the left lower leg because of a past fracture, and varicose veins were observed on both legs.

Laboratory examination revealed a white blood cell count of 9,300/µl with 24% neutrophils, 1% band form, 8% eosinophils, 5% monocytes, and 62% lymphocytes. Hemoglobin was 12.9 g/dl, and the platelet count was 66,000/µl. Platelet clumping was observed by microscopic observation (Fig. 1). AST, ALT, and LDH were all normal. BUN and serum creatinine were 14 mg/dl and 0.7 mg/dl, respectively. Uric acid was 2.6 mg/dl. Total protein was 6.9 g/dl, IgG, 1.252 mg/dl, IgA, 83 mg/dl, and IgM, 98 mg/dl. C-reactive protein (CRP) was 0.1 mg/dl, and the rheumatoid factor was negative. Antinuclear, anti-DNA, and anti-ENA antibodies were all negative. A hormonal study revealed hypogonadism, since testosterone was 0.7 ng/ml (normal range: 4.1–11.0), dehydroepiandrosterone (DHEA) was below 200 ng/ml (normal range: 500–3,000), and androsterone was 0.068 ng/ml (normal range: 0.175–0.910). Basal gonadotropins, as measured by radioimmunoassay, were increased at an LH level of 75 U/l (normal range: 2–32), and an FSH level of 73 U/l (normal range: 4–42). After an injection of 100 µg gonadotropin-releasing hormone (LH-RH), the LH level rose to 360 U/l at 90 min, and FSH increased to 160 U/l at 60 min. The prolactin (PRL) level was 11 ng/ml as a basal level, which rose to 100 ng/ml after intravenous injection of 500 µg TRH. TSH level was 1.4 µU/ml, and rose to 4.8 µU/ml 30 min after TRH administration. Chromosome analysis demonstrated that twenty out of twenty-five peripheral lymphocytes showed 48, XXYY karyotype without translocation, and the remaining five were 47, XXY karyotype according to the G-banding method (47 XXY/48 XXYY mosaicism) (Fig. 2).

The platelet count, measured with an electric counter (Coulter FN, Coulter Electrics, Inc), was 66,000/µl when anticoagulated with EDTA, and 199,000/µl with heparin anticoagulation. EDTA-treated plasma from the patient induced a clumping of the platelets from normal healthy individuals, indicative of the diagnosis of EDTA-dependent pseudothrombocytopenia.

Platelet agglutinin was analyzed by indirect immunofluorescent study. Normal heparin-treated platelet-rich
plasma was washed three times with veronal buffer (pH 7.4), and suspended in 1% bovine serum albumin and smeared on a glass slide. The patient’s EDTA-treated plasma was reacted with normal platelets in the smear at room temperature for 60 min. The smear was then washed twice with phosphate-buffered saline for 15 min, and was reacted with FITC-conjugated goat anti-human IgG, IgA, IgM, kappa, and lambda antibodies (Behringwerge, Germany) at 37°C for 30 min. Pooled EDTA-treated plasma from normal healthy individuals was used as a control.

IgM and kappa stained positive in the platelets reacted with EDTA-plasma from the patient, however, staining by anti-IgG, IgA, lambda antibodies was completely negative. None of the FITC anti-human IgG, IgA, IgM, kappa, or lambda antibodies were stained the platelets treated with EDTA-plasma from normal healthy individuals.

Discussion

The present case of 48, XXYY syndrome accompanied by pseudothrombocytopenia was also associated with hypouricemia. The 48, XXYY syndrome was first reported by Mudal and Ockey (1) in 1960 as a “double male” syndrome, and placed in the category of Klinefelter’s syndrome with the 47, XXY chromosome. Jacobs et al (11) in 1965 demonstrated that patients with XYY syndrome have aggressive behavior and mental subnormality. In 1970, Parker et al (2) emphasized that the 48, XXYY syndrome should be classified as a separate entity from Klinefelter’s and the XYY syndromes on the basis of physical, dermatographic, mental, and hormonal differences. Physical and laboratory findings of the three syndromes are summarized in Table 1. The data obtained from the present case are in agreement with that reported by other investigators (3). The 48, XXYY syndrome has endocrine characteristics that are higher than normal basal levels of LH and FSH, with a hyperresponse of LH and FSH after LH-RH administration. In general, the differentiation of the neutral gonad into testis is well known to depend on the histocompatibility Y antigen A (HYA), produced by an activated gene on Y chromosome (12). In the 48, XXYY syndrome, the determination of sex is controlled by HYA on the Y chromosome. However, the insufficient formation of the male phenotype, or hypogonadism, is derived from the excess of X chromosomes. The “supermale” with an excess of Y chromosomes is reported to have aggressive behavior by Jacobs et al (11). Although several investigators described that the 48, XXYY syndrome also causes an aggressive personality similar to the XYY syndrome (13, 14), the present patient did not show aggressive behavior, despite having induced many problems in hospital. This finding suggests that the aggressiveness depends on familial and social environment, rather than on a specific character of the 48, XXYY syndrome (15).

The present patient showed hypouricemia with a level of 2.6 mg/dl (normal range: 3.2–7.5). The 48, XXYY syndrome associated with hypouricemia has been described by Nakajima et al (15), who suggest that both diseases are coincidental. In their study, the patient’s brother with normal chromosome constitution also had hypouricemia due to renal tubular hypersecretion of uric acid. Because family studies and oral administration tests of probenecid and pyrazinamide were not performed in the present study, the cause of hypouricemia could not be determined.

Regarding EDTA-dependent pseudothrombocytopenia, pseudothrombocytopenia is classified into two types: one is platelet clumping (agglutination), and the other is platelet adhesion to polymorphonuclear leuko-

| Table 1. Characteristics of Klinefelter's, the 48, XXYY and the XYY Syndromes |
|-------------------------------------------------|-----------------|------------------|------------------|
| Karyotype                                       | 47, XXY         | 48, XXYY         | 47, XYY          |
| Height                                          | normal          | tall             | tall             |
| Hypogonadism                                    | presence        | presence         | absence          |
| Testes                                          | small           | small            | normal           |
| Pubic hair                                      | sparse          | 50               | normal           |
| Gynecomastia (%)                                | 20-30           | 0                | 0                |
| Abnormal habitus                                 | funnel chest, cervical rib, scoliosis | webbed neck, fusions of radial and ulner bones, tibial and fibral bones | Marfan's syndrome like statue |
| Intelligence                                    | 75% normal      | moderate to severe retardation | normal          |
| Personality                                     | passive, introvert | aggressive (?) , not-cooperative | aggressive, abnormal behaviour |
| Incidence                                       | 1 in 1,000 newborn males | 1 in 50,000 newborn males | 1 in 1,000 newborn males |
| Endocrine                                       | 17 KS low       | low              | low              |
|                                                | LH normal (slightly elevated) | extremely elevated | normal           |
|                                                | FSH elevated    | extremely elevated | normal           |
cytes (platelet satellitism). Platelet agglutinin is commonly known as IgG, IgA, and IgM. Several investigators have shown that platelet agglutinin reacted with GPIIb/IIIa (16, 17), or GPIb (17), or other unknown antigens (17) found on the platelet surface in the presence of EDTA. Pseudothrombocytopenia can be observed not only in normal healthy individuals, but in patients with malignancies (4, 5), acute and chronic liver disease (6, 7), some autoimmune diseases (4, 8, 9), and chronic glomerulonephritis (10). The present case exhibited both EDTA-dependent pseudothrombocytopenia and the 48, XXYY syndrome, which showed the mosaicism of 48, XXYY and 47, XXY chromosome in peripheral lymphocytes. Although this combination may be purely circumstantial, the possibility that the mosaicism of lymphocytes may produce platelet agglutinin remains to be clarified.

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References