UNFORESEEN DETECTION OF KLINEFELTER SYNDROME DURING THE MANAGEMENT OF LUPUS NEPHRITIS IN AN ADOLESCENT—A CASE REPORT

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Abstract

Autoimmune disease is common in males with Klinefelter syndrome (KS) as testosterone deficiency predisposes them to the disease. A 20-year-old male who was diagnosed with lupus nephritis and he presented with bilateral progressive gynecomastia associated with signs of hypogonadism. Further workup confirmed the incidental diagnosis of Klinefelter syndrome (KS). This case illustrates the importance of investigating the cause of hypogonadism in males with autoimmune disease as early treatment with testosterone therapy can be beneficial in treating the clinical disease and preventing complications.

Keywords: Autoimmune disease; Klinefelter syndrome; Lupus nephritis
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Introduction

SLE is an autoimmune disease that affects females aged 20 to 30 years, while in male, the age of onset is between 45 to 60 years old [1]. Male with KS has a higher incidence of autoimmune diseases such as Systemic lupus erythematosus (SLE), Addison disease, multiple sclerosis, Rheumatoid arthritis and Sjogren syndrome compared to the normal male population as they have higher estrogen levels which is believed to be immunostimulant in nature [2].

KS is a condition whereby a male has an extra X chromosome with phenotype of hypergonadotropic hypogonadism, gynecomastia, infertility and underdeveloped genitalia. Reduced testosterone levels with contrasting increase in estrogen levels predispose males with KS to develop autoimmune diseases as estrogen stimulates the immune system while testosterone was proved to be immunosuppressed [4]. The extra X chromosomes in Klinefelter syndrome cause the prevalence of SLE to increase by 14-fold [1]. In contrast, the prevalence of SLE in Turner syndrome is lower compared to other diseases such as autoimmune thyroid disease, Crohn’s disease and celiac disease as this could be related to gene dose effect [5].

Treatment of lupus nephritis is mainly using immunosuppressants with monoclonal antibody and antiproteinuric agent. However, in males with KS, the use of testosterone replacement therapy is mandatory as it proves to reverse and prevent complications such as underdeveloped genitalia, gynecomastia, testicular atrophy and insulin resistance syndrome (diabetes mellitus, fatty liver disease, peripheral vascular disease and dyslipidemia) [14].

Case presentation

A 20-year-old male was diagnosed with SLE and lupus nephritis at the age of 10 whereby he presented with generalized rashes and prolonged fever. His blood results showed leucopenia, thrombocytopenia, nephrotic range proteinuria and a positive immunological test (shown in Table 1). His skin biopsy revealed leukocytoclastic vasculitis, while his renal biopsy was consistent with class IV lupus nephritis (Original Whole Health Organization Classification of lupus nephritis 1974). He had been commenced on...
Intravenous (IV) methylprednisolone followed by IV cyclophosphamide but he did not achieve remission. Oral cyclosporin was started, however, he developed gum hypertrophy and hirsutism as side effect. Treatment was stopped and changed to Mycophenolate mofetil, prednisolone and oral hydroxychloroquine. He achieved remission in one year and immunosuppressant was gradually weaned off. However, he again showed clinical relapse after 10 months post treatment. Following that, he was restarted back on a combination of Mycophenolate mofetil and Hydroxychloroquine.

<table>
<thead>
<tr>
<th>Labs</th>
<th>Value</th>
<th>Unit</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular Stimulating Hormone (FSH)</td>
<td>43.97</td>
<td>IU/L</td>
<td>1.5 – 12.4</td>
</tr>
<tr>
<td>Luteinizing hormone (LH)</td>
<td>18.87</td>
<td>IU/L</td>
<td>1.7 – 8.0</td>
</tr>
<tr>
<td>Estradiol</td>
<td>64.77</td>
<td>pmol/L</td>
<td>41 – 159</td>
</tr>
<tr>
<td>Testosterone</td>
<td>6.39</td>
<td>nmol/L</td>
<td>8.64 – 29.0</td>
</tr>
</tbody>
</table>

He had progressive bilateral breast enlargement since the age of 16-year-old (Picture 1&2) with height was at between the 5th to 10th centile and weight was between the 10th to 25th centile. His Body Mass Index (BMI) was documented as 21kg/m² with truncal obesity and fat deposition at the hip. Further examination showed Tanner staging 3 (B3 A2 P3). His Stretched Penile Length (SPL) was 8cm. The external urethral meatus was at the tip of penis. His testes were soft in consistency with a volume of 4 ml.

Diagnosis of hypergonadotrophic hypogonadism was confirmed with Luteinizing Hormone Releasing Hormone test which showed higher FSH compared to LH. The differential diagnosis was drug-induced gynecomastia, cyclophosphamide toxicity, aromatase excess syndrome and Klinefelter syndrome. Karyotyping result showed 47 XXY confirming the diagnosis of Klinefelter syndrome. He received oral tamoxifen 20mg twice daily, subcutaneous human Menopausal Gonadotropin (hMG) and Intramuscular (IM) testosterone monthly which have failed to regress his condition. After a discussion with the family, they agree for breast reconstructive surgery. He continued to receive monthly IM testosterone and immunosuppressant, his SLE status was in remission and dsDNA were less than 50 IU/ml.

**Discussion**

Klinefelter syndrome is a genetic disorder which often is under diagnosed as it has high variability in clinical presentations [8]. Most patients presented with underdeveloped testes, hypergonadotrophic hypogonadism, gynecomastia and infertility. Shiari and Farivar reported a 14-year-old boy presented with leg ulcers and arthritis [6]. In our case, the diagnosis of SLE and lupus nephritis were made from ANA positivity and mesangial glomerulonephritis on renal biopsy. His co- incidental findings of Klinefelter syndrome was confirmed by karyotyping and endocrine workups. Immunosuppressant and testosterone were seen to improve his symptoms [6]. Similar case was described by Cox and Marguerie in 2017 [7] Where a 37-year-old man was found to have testicular atrophy and reduced body hair. The blood tests showed the feature of pancytopenia and...
transaminitis. Chromosomal analysis from bone marrow aspiration showed 47XXY. He was labelled as autoimmune hepatitis, SLE, Sjögren syndrome and with incidental findings of Klinefelter syndrome.

The striking feature of Klinefelter syndrome in this patient is from the presence of progressive bilateral gynecomastia. He was taking enalapril and prednisolone where gynecomastia could potentially be one of the side effects [9]. Careful examination of the patient revealed further signs of hypogonadism such as truncal obesity, fat deposition at the hip and small testes volume. The causes of hypogonadism are multifactorial. Cyclophosphamide use could damage germ cells in seminiferous tubules affecting spermatogenesis and Leydig cells leading to low testosterone production [10]. Aromatase excess syndrome is also one of the differential diagnoses for his symptoms as it consists of gynecomastia, accelerated bone age, short stature and hypogonadotropic hypogonadism. Unfortunately, this was absent in this patient [11]. Karyotyping is an important investigation for Klinefelter syndrome diagnosis.

For lupus nephritis, treatment includes immunosuppressants such as IV methylprednisolone, oral cyclosporin, mycophenolate mofetil, IV cyclophosphamide and monoclonal antibody [12]. In male patients with Klinefelter syndrome, testosterone therapy is required. In some case reports, patients were shown to achieve good treatment response and remission from autoimmune disease after testosterone therapy [6-7]. Testosterone was shown to influence the immune system in Klinefelter syndrome patients [13]. Early detection of hypogonadism is important for induction of remission by the use of testosterone. To date, there was no study to report the benefit of testosterone along with immunosuppressants in earlier remission induction.

Conclusion
Males with autoimmune diseases should undergo a thorough and careful clinical examination if there is a presence of abnormal pubertal progression, in order to rule out underlying hypogonadism. Early detection and treatment are essential to avoid further complications.

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Conflict of interest
The authors have no conflict of interest to declare.

Ethical approval
Verbal informed consent for publication was taken from the patient who has a full capacity.

References


