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Case Report

Internal Medicine Section

Delayed Diagnosis of 48, XXYY Syndrome in an Adult Male Presenting with Severe Insulin Resistance and Hypergonadotropic Hypogonadism: A Case Report

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ABSTRACT

A 48,XXYY syndrome is a rare sex chromosome aneuploidy affecting 1 in 18,000 to 50,000 male births. While metabolic dysfunction is a recognised feature, most adult cases are identified during evaluations for cognitive difficulties, delayed puberty, or infertility. Initial adult presentation through extreme insulin resistance and striking dermatological markers remains highly unusual. We report a 34-year-old male presenting with a one-year history of poorly controlled diabetes and progressive hyperpigmented, scaly skin lesions. Physical examination revealed a body mass index of 28.4 kg/m^2, a waist circumference of 101 cm, sparse body hair, long-standing grade III gynaecomastia, and small bilateral testes. Dermatological assessment confirmed extensive acanthosis nigricans across the neck and axillae, paired with widespread dermatomycosis. Despite a high-dose basal-bolus insulin regimen of 90 units daily combined with four oral antidiabetic agents, severe hyperglycaemia persisted (HbA1c: 10.2%, fasting blood glucose: 320 mg/dL). Endocrine evaluation indicated primary hypergonadotropic hypogonadism, marked by low total testosterone (150 ng/dL) alongside elevated follicle-stimulating hormone (42.77 mIU/mL) and luteinising hormone (43.91 mIU/mL). A C-peptide level of 2.1 ng/mL verified preserved beta-cell function. Subsequent peripheral blood cytogenetic analysis confirmed a 48,XXYY karyotype. The patient was referred for testosterone replacement therapy, bone density monitoring, and fertility counselling. This case underscores the necessity of considering underlying sex chromosome aneuploidies in adult males who exhibit unexplained primary hypogonadism alongside highly refractory metabolic disease, ensuring timely access to essential multidisciplinary interventions.

Keywords: Chromosome aberrations, Karyotype, Sex chromosome disorders

CASE REPORT

A 34-year-old male presented to the Department of General Medicine with a 10-month history of polyuria, polydipsia, and fatigue, alongside progressive skin changes over the past four months. He had a one-year history of poorly controlled type 2 Diabetes Mellitus, which had been managed with metformin alone up to this point. There was no parental consanguinity, and the family history was completely negative for diabetes or known chromosomal disorders.

His symptoms began with a four-month history of progressive, hyperpigmented, scaly skin lesions that originated on his face before spreading to his back and shoulders. He also reported a 15-year history of reduced libido and bilateral gynaecomastia that had never undergone medical evaluation. The patient reported no history of delayed puberty, learning disabilities, or behavioural disorders, and all childhood developmental milestones were normal.

On general examination, height was 178 cm, weight 90 kg, body mass index 28.4 kg/m^2, waist circumference 101 cm, hip circumference 107 cm, giving a waist-to-hip ratio of 0.94 (indicative of central adiposity). Blood pressure was 130/80 mmHg and pulse 87 beats per minute. Skin examination with a dermatologist identified acanthosis nigricans involving the neck and axillae, and dermatomycosis producing hyperpigmented scaly plaques over the face [Table/Fig-1], back [Table/Fig-2], and shoulders [Table/Fig-3]. No mycological confirmation was performed; the diagnosis was established clinically. Systemic examination revealed bilateral grade III gynaecomastia with marked breast enlargement and prominent skin redundancy, classified according to the Simon grading system, alongside noticeable truncal adiposity [1]. Gynaecomastia had been present for 15 years without prior medical evaluation. Written informed consent was obtained from the patient for publication of this image [Table/Fig-4]. Genitalia showed a small penis with bilateral small testes, confirmed by ultrasonography (right 7 mL, left 5 mL) [Table/Fig-5]. Tanner staging was stage IV. Sparse facial and body hair was noted throughout.



[Table/Fig-1]: Hyperpigmented, scaly plaques over the malar and periorbital regions, clinically confirmed as dermatomycosis of 4-month duration.



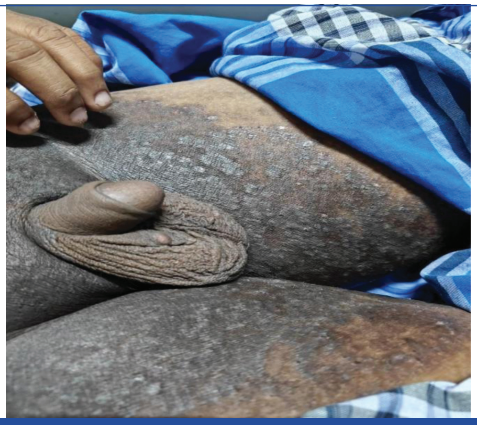
[Table/Fig-2]: Extensive hyperpigmented scaly plaques over the upper and mid-back, consistent with dermatomycosis. Lesions had been present for five months.



[Table/Fig-3]: Hyperpigmented scaly lesions over the shoulders, continuous with the back lesions shown in [Table/Fig-2], forming part of the widespread cutaneous involvement that prompted dermatological consultation.



[Table/Fig-4]: Bilateral grade III gynaecomastia with truncal adiposity. Gynaecomastia had been present for 15 years without prior medical evaluation.



[Table/Fig-5]: Bilateral small testes on genital examination. Ultrasonography confirmed testicular volumes of 7 mL (right) and 5 mL (left), consistent with primary testicular failure.

Therapy was intensified to a basal-bolus insulin regimen combined with metformin, sitagliptin, voglibose, and glimepiride. However, glycaemic control remained poor despite a high maximum daily insulin dose. Severe insulin resistance was inferred clinically from the high insulin requirement, preserved beta-cell function, persistent hyperglycaemia, and extensive acanthosis nigricans; fasting insulin and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) were not measured.

Endocrine evaluation confirmed primary hypergonadotropic hypogonadism, characterised by depressed total and free testosterone levels alongside significantly elevated follicle-stimulating hormone and luteinising hormone. Prolactin was mildly elevated, while thyroid function was completely normal. Estradiol and sex hormone-binding globulin were not measured. Subsequent peripheral blood cytogenetic analysis confirmed a sex chromosome aneuploidy with a 48,XXYY karyotype. Metabolic, endocrine, and lipid values are summarised in [Table/Fig-6].

Parameters	Value	Reference range	Interpretation
Fasting blood glucose (mg/dL)	320	70-110	Elevated
Postprandial blood glucose (mg/dL)	442	<140	Elevated
HbA1c (%)	10.2	4.0-5.6	Poor glycaemic control
C-peptide (ng/mL)	2.1	0.8-3.85	Preserved beta-cell function
Maximum insulin dose (units/day)	90	N/A	Severe insulin resistance (clinical)*
Total testosterone (ng/dL)	150	300-1000	Low
Free testosterone (pg/mL)	1.70	5-21	Low
FSH (mIU/mL)	42.77	1-12	Elevated
LH (mIU/mL)	43.91	1-9	Elevated
Prolactin (ng/mL)	23.47	2-18	Mildly elevated
TSH (mIU/L)	0.87	0.4-4.0	Normal
Free T4 (ng/dL)	1.01	0.8-1.8	Normal
Total cholesterol (mg/dL)	200	<200	Borderline high
LDL cholesterol (mg/dL)	133	<130	Above diabetic target†
HDL cholesterol (mg/dL)	44	>40	Normal
Triglycerides (mg/dL)	153	<150	Mildly elevated
VLDL (mg/dL)	35	<30	Mildly elevated
Karyotype	48,XXYY	46,XY	Sex chromosome aneuploidy

[Table/Fig-6]: Endocrine, metabolic, and related laboratory findings.
*Severe insulin resistance inferred clinically from high insulin requirement, preserved C-peptide, persistent hyperglycaemia, and acanthosis nigricans; fasting insulin and HOMA-IR were not measured; †LDL target for patients with diabetes is <100 mg/dL per current guidelines
FSH: Follicle-stimulating hormone; HbA1c: Glycated haemoglobin; HDL: High-density lipoprotein; HOMA-IR: Homeostatic model assessment of insulin resistance; LDL: Low-density lipoprotein; LH: Luteinising hormone; VLDL: Very low-density lipoprotein

The combination of severe insulin resistance, primary hypergonadotropic hypogonadism, gynaecomastia, sparse body hair, and small testes raised suspicion of a sex chromosome disorder. Differential diagnoses included Klinefelter syndrome (47,XXY), other causes of primary hypergonadotropic hypogonadism, and endocrine causes of severe insulin resistance. Conventional peripheral blood karyotyping (G-banding, 72-hour phytohaemagglutinin-stimulated cultures; Anderson Diagnostics) confirmed a 48,XXYY karyotype comprising 48 chromosomes with two X and two Y sex chromosomes. The patient was referred to Endocrinology for testosterone replacement therapy following fertility counselling. Bone health assessment and long-term multidisciplinary follow-up were planned. Testosterone therapy had not been initiated during this admission.

DISCUSSION

This patient presented at the age of 34 with severe insulin-resistant diabetes, acanthosis nigricans, dermatomycosis, grade III gynaecomastia of 15 years' duration, bilateral small testes, sparse body hair, and markedly elevated gonadotropins with low testosterone. Glycaemic control remained highly suboptimal despite initial metformin therapy and a subsequent in-hospital transition to an intensive basal-bolus regimen involving four antidiabetic agents. Even as daily insulin requirements escalated to 90 units, the patient's metabolic state did not improve. A preserved C-peptide level demonstrated that peripheral insulin resistance, rather than beta-cell exhaustion, was the driving pathophysiological mechanism. These atypical metabolic findings prompted a cytogenetic evaluation, which ultimately identified a 48,XXYY karyotype. Interestingly, his long-standing gynaecomastia and classic hypogonadal features had never been linked to an underlying genetic condition. This diagnostic gap highlights the prolonged recognition delays frequently seen when 48,XXYY syndrome presents in adulthood.

Rather than being a simple variation of classic 47,XXY Klinefelter syndrome, 48,XXYY syndrome represents a distinct sex chromosome

aneuploidy that affects roughly 1 in 18,000 to 50,000 male live births [2-4]. While primary hypergonadotropic hypogonadism is a core feature of both conditions, the 48,XXYY phenotype involves a more severe clinical burden. This includes higher rates of neurodevelopmental difficulties, intentional tremors, peripheral vascular skin changes, and a significantly elevated risk of developing adult-onset type 2 diabetes [2,5].

Published adult cases with diabetes include a man with insulin-treated diabetes, elevated gonadotropins, and small testes [6]; a 43-year-old French man with type 2 diabetes and gonadal dysfunction [7]; a 45-year-old Tunisian man with type 2 diabetes, metabolic syndrome, and pigmentary retinitis [8]; an adult American man reassessed from a prior Klinefelter diagnosis with metabolic syndrome [9]; and a 34-year-old Indian man with primary infertility and type 2 diabetes [10]. A recent American report described a 26-year-old with insulin-requiring diabetes and 48,XXYY who was tall and thin, lacked acanthosis nigricans, and had no metabolic syndrome features, illustrating phenotypic heterogeneity in glucose dysregulation [11]. Several adult cases have been identified through infertility workup [12] or obesity and psychiatric referral [13] rather than through metabolic investigation. The present case, therefore, belongs to a small metabolic-endocrine subgroup of adult XXYY presentations diagnosed through refractory diabetes with overt insulin-resistance markers.

The metabolic phenotype is likely multifactorial. Testosterone deficiency from primary testicular failure promotes visceral adiposity and insulin resistance, a relationship well established in Klinefelter syndrome, where androgen deficiency independently predicts metabolic syndrome and type 2 diabetes [14,15]. However, androgen deficiency alone does not fully account for the severity of insulin resistance observed. Gene-dosage studies show that supernumerary X-chromosome material alters adiposity, lipid metabolism, and insulin signalling independently of gonadal hormones [16-18]. A cross-sectional study of high-grade sex chromosome aneuploidies found worse body weight, lipid profiles, and post-load glucose tolerance compared with classic 47,XXY, supporting a chromosomal dosage effect that extends beyond hypogonadism [19]. While a mild elevation in prolactin levels might have added a minor metabolic burden, it cannot account for the sheer severity of this patient's metabolic derangement. Instead, the preserved C-peptide level serves as clear confirmation that peripheral insulin resistance stands as the primary physiological defect.

When contrasted with classic 47,XXY Klinefelter syndrome, the 48,XXYY phenotype is typically characterised by an earlier onset of severe gonadal dysfunction, a higher burden of cognitive or behavioural challenges, and a greater frequency of both vascular and dermatological anomalies [2,4,5]. Interestingly, acanthosis nigricans is rarely highlighted in the existing literature on adult 48,XXYY skin presentations, which overwhelmingly focus on peripheral vascular changes and severe acne [2,5,20]. In this specific clinical scenario, the extensive acanthosis nigricans served as a highly visible indicator that pointed directly toward an underlying endocrine and metabolic pathology. Meanwhile, the concurrent dermatomycosis simply illustrated the predictable cutaneous complications of long-term, uncontrolled hyperglycaemia. The fact that this distinct hypogonadal phenotype went unacknowledged throughout 15 years of lived gynaecomastia and during a full year of active diabetes management highlights a known diagnostic hurdle. No isolated physical feature in 48,XXYY typically prompts a genetic workup on its own; a definitive diagnosis generally depends on a clinician's ability to patch together scattered endocrine, reproductive, and dermatological clues [10-12].

Because condition-specific clinical guidelines for 48,XXYY do not exist, current management strategies rely on standard Klinefelter syndrome protocols that are manually tailored to address the broader complications of the XXYY phenotype [2,21]. Initiation of testosterone replacement therapy is currently planned. While this intervention can optimise body composition and improve systemic insulin sensitivity, clinicians should recognise that androgen therapy alone is unlikely to fully resolve underlying diabetes mellitus [14,15,22]. Reproductive counselling is an essential next step. Although the overall likelihood of successful sperm retrieval is quite low in patients with a 48,XXYY karyotype, testicular sperm extraction remains an option worth discussing [2]. Comprehensive ongoing care must include formal bone density testing, vitamin D screening, and structured, multi-specialty surveillance involving endocrinologists, geneticists, reproductive specialists, and internal medicine physicians [21,22]. A formal psychiatric evaluation was deferred during the acute presentation due to a lack of overt behavioural or cognitive symptoms. Nevertheless, specialised neurobehavioural tracking should remain part of the long-term care plan because of the high baseline prevalence of neuropsychiatric issues in this population [2,5]. Several limitations affect this case report, notably the lack of baseline fasting insulin levels, calculated HOMA-IR indices, estradiol measurements, sex hormone-binding globulin tracking, and a baseline semen analysis. Furthermore, this report lacks longitudinal follow-up data and does not include advanced cytogenetic testing details beyond standard karyotyping.

CONCLUSION(S)

This case highlights a rare instance of an adult 48,XXYY syndrome diagnosis triggered by severe, insulin-resistant diabetes and extensive acanthosis nigricans, deviating from the typical diagnostic routes of infertility or neurobehavioural delays. Physicians managing adult male patients who present with highly refractory metabolic disorders should maintain a high index of suspicion for underlying sex chromosome aneuploidies if primary hypergonadotropic hypogonadism is present alongside suggestive phenotypic markers, regardless of whether fertility is an active concern. Establishing an early cytogenetic diagnosis is vital, as it allows for the prompt initiation of hormone replacement, aggressive metabolic control, and coordinated multidisciplinary care.

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