

CASE REPORT

Macrogonadotropinoma, a venous thromboembolic event and asymptomatic extensive periventricular white matter changes in a patient with Klinefelter syndrome

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Abstract

Gonadotropinoma in Klinefelter syndrome (KS) is uncommon and may be a result of protracted stimulation of gonadotrophs from lack of androgen feedback. Associations of white matter changes and increased venous thromboembolic risk have been reported and need to be considered in patients with KS.

KEYWORDS

Klinefelter syndrome, macrogonadotropinoma, periventricular white matter changes, pulmonary embolism, venous thromboembolism

1 | INTRODUCTION

Klinefelter syndrome (KS) is a genetic disorder marked by the presence of two or more X chromosomes in males, leading to primary hypogonadism, generally requiring androgen therapy. Coexisting pituitary adenomas, including gonadotropinomas, are rare, but have been reported.¹

Gonadotropinomas are generally regarded as nonfunctioning adenomas, but in our case, gonadotroph secretion becomes clinically relevant. A very few KS cases have been reported to have extensive white matter changes, most being associated with the more severe 48XXXY phenotypes, and others have reported gray matter changes.²

Klinefelter syndrome patients have an intrinsically higher VTE risk than the general population, and their thrombotic risk should be considered in this setting.³

This higher risk, along with probable coexisting thrombophilic mutations/polymorphisms, further predisposes KS patients to thrombotic events without an obvious clinical event. Hence, there is a need to develop protocols for screening and prophylaxis of VTE in KS.

2 | CASE PRESENTATION

A 57-year-old male, while undergoing evaluation for tinnitus, was found to have a pituitary macroadenoma on MRI. He was subsequently referred to a neurosurgeon and an endocrinologist. There were no new symptoms of hormonal imbalance. He was known to have karyotypically confirmed nonmosaic KS, diagnosed in his third decade while undergoing evaluation for infertility. Despite being azoospermic, he had normal

testosterone levels and had never required replacement. He had mild dyslipidemia treated with a lipid-lowering agent. He was a nonsmoker and did not consume alcohol. Physical examination revealed classic anthropomorphic features of KS, with a tall stature of 187 cm and relatively short trunk, bilateral gynecomastia, an arm span not exceeding height, a weight of 80 kg, and a BMI of 22.9 kg/m². There were no visual field defects or clinical signs of androgen deficiency.

3 | INVESTIGATIONS

Initial laboratory endocrine evaluation was within normal limits (Table 1). Formal visual field testing was normal; however, on optical coherence tomography there was subtle thinning of the retinal ganglion cell layer at the macula bilaterally. MRI showed a pituitary macroadenoma measuring 15 × 20 × 17 mm (Figure 1). There were also extensive periventricular white matter changes on the MRI (Figure 2). Screening for adrenoleukodystrophy and vasculitis did not reveal any significant abnormality. Carotid Doppler ultrasound was normal. Chromosomal testing confirmed a 47 XXY karyotype consistent with KS. Ultrasound of the testes showed reduced volume bilaterally (2 mL).

4 | TREATMENT

Our patient proceeded to have a transsphenoidal adenectomy (TSA). Due to its close proximity to the cavernous sinus, there was incomplete resection of the adenoma, with 5 mm residual tissue (Figure 3). Postoperatively, he had partial hypopituitarism and was commenced on hydrocortisone and thyroxine replacement.

5 | OUTCOME AND FOLLOW-UP

The histopathology was consistent with a pituitary macroadenoma with positive immunohistochemistry for FSH and to a lesser extent LH and negative for other hormones. Following the TSA, he had annual pituitary hormone evaluation, which showed persistent elevation of FSH and LH, but normal testosterone levels (Tables 2 and 3). Insulin-like growth factor (IGF)-1 level was also raised but had adequate suppression of growth hormone following a glucose load (Table 2). Surveillance MRIs showed slow growth of residual tumor over the next 5 years, to a maximum diameter of 10 mm, without optic chiasm compression or visual symptoms (Figure 4). Multidisciplinary case discussion recommended stereotactic radiotherapy to the slow-growing residual tumor, although this has not been performed yet. At outpatient review, 6 months later, our patient reported symptoms of exertional dyspnoea and a computed tomography pulmonary angiogram

TABLE 1 Preoperative endocrine laboratory evaluation

Pituitary profile	Result	Reference range
FSH	19.3 U/L	1.0-10.0
LH	7.2 U/L	2.0-12.0
Testosterone	11.2 nmol/L	9.5-28.0
IGF-1	16.0 nmol/L	11.0-29.0
ACTH	11.0 pmol/L	0.0-12.0
Morning cortisol	392 nmol/L	138-650
Prolactin	204 mIU/L	<330
TSH	1.85 mIU/L	0.40-4.00
T3/T4	3.5/10.3 pmol/L	2.6-6.0/9.0-19.0
Osmolality	301 mOsm/kg	275-295
Chromosomal testing	47XXY	>15 cells reviewed

Abbreviation: ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; IGF-1, insulin-like growth factor 1; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

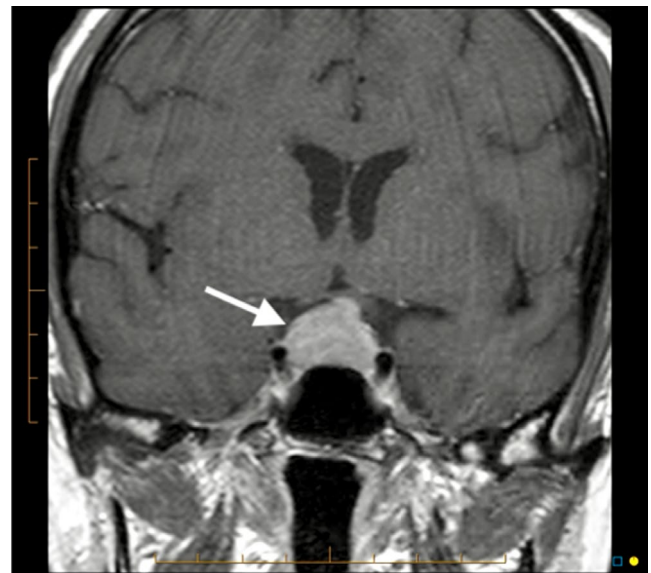


FIGURE 1 Preoperative MRI showing pituitary adenoma measuring 15 × 20 × 17 mm

(CTPA) showed the presence of multiple bilateral pulmonary emboli, in the absence of a triggering event. A CT of his chest, abdomen, and pelvis excluded occult malignancy. Screening for inheritable thrombophilia showed heterozygous mutation of the factor V Leiden gene. He was commenced on therapeutic anticoagulation with a factor Xa inhibitor, rivaroxaban.

6 | DISCUSSION

Three aspects of the case will be examined:

The presence of persistent elevation of gonadotropin levels in a patient with minimal

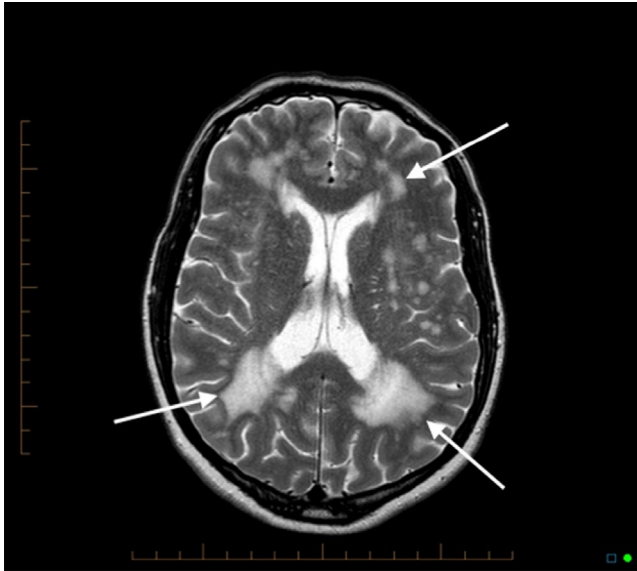


FIGURE 2 Incidental extensive periventricular white matter changes

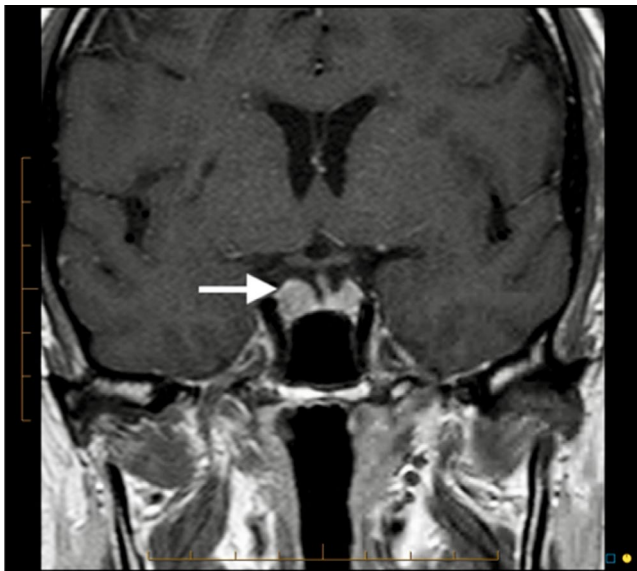


FIGURE 3 Immediate postoperative pituitary MRI showing right sided 5 mm residual tumor

manifestations of his genetic syndrome and who has never required androgen replacement therapy.

From an endocrinological standpoint, patient symptoms, clinical signs, and biochemistry vary. In the large cohorts of described patients, there is 100% FSH elevation and only about 80% LH elevation, with 50% of the patients with normal LH, having a normal testosterone.⁴ This could be explained by what seems to be a preferential change to the function of germinal epithelium and Sertoli cells of the testes instead of, only moderately reduced to normal function of the Leydig cells as per the original description by Klinefelter

TABLE 2 Five-year postoperative endocrine laboratory evaluation

Pituitary profile	Result	Referenced range
FSH	47.6 U/L	1.0-10.0
LH	19.2 U/L	2.0-12.0
Testosterone	14.5 nmol/L	9.5-28.0
SHBG	47 nmol/L	10.0-73.0
FAI	29.8	35.0-85.0
Prolactin	200 mIU/L	<330
Morning cortisol	296 nmol/L	138-650
ACTH	4.0 pmol/L	0.0-12.0
IGF-1	40 nmol/L	11.0-29.0
Growth hormone response to 75 g glucose	Glucose levels	Growth hormone
0 min	4.9 mmol/L	5.1 mU/L
60 min	5.5 mmol/L	0.6 mU/L
120 min	3.1 mmol/L	0.5 mU/L
180 min	3.9 mmol/L	1.7 mU/L

Abbreviation: ACTH, adrenocorticotropic hormone; FAI, free androgen index; FSH, follicle-stimulating hormone; IGF-1, insulin-like growth factor 1; LH, luteinizing hormone; SHBG, sex hormone-binding hormone; TSH, thyroid-stimulating hormone.

et al in 1942.⁵ Despite partial hypopituitarism following the TSA and requiring thyroid and cortisol axes replacement, our patient has persistently raised FSH and postoperative LH gonadotropin levels. This may be secondary to hypersecretion of gonadotropins from the residual gonadotropinoma contributing to maintain testosterone levels or reactive pituitary hyperplasia secondary to long-standing relative androgen insufficiency.

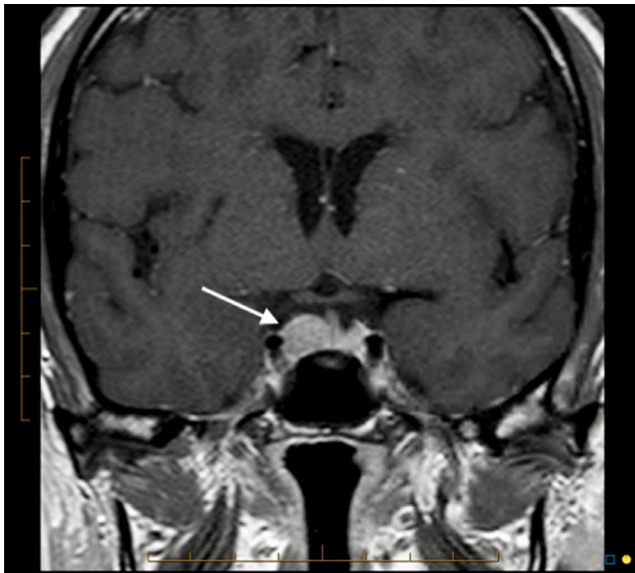
Gonadotropinoma in KS is rare. In a case series of 3 patients with primary hypogonadism, 2 had gonadotroph hyperplasia.⁶ The third case was a 76-year-old with KS, confirmed on genetic testing, with a large sellar mass resected by transsphenoidal surgery. The histopathology showed an oncocytic gonadotroph macroadenoma, immunoreactive for FSH and alpha-subunit. No information was available regarding whether he required testosterone replacement. One case report describes a gonadotropinoma in a man with long-standing hypogonadism, which was immunoreactive for FSH and LH.¹ Similar to our case, the pathology could perhaps be explained by protracted stimulation of gonadotrophs resulting in hyperplasia and subsequent development of a macrogonadotropinoma. This raises the question as to whether a trial of testosterone replacement therapy would help shrink the gonadotropinoma, similar to the principle of thyroxine therapy to suppress residual thyroid cancer.

The presence of extensive white matter changes without overt clinical manifestations and only one vascular risk factor (dyslipidaemia).

TABLE 3 Table showing trend of FSH, LH, testosterone, and IGF-1 over 5 years

Pituitary profile	Initial	Postoperative years						Reference range
		0.5	1	2	3	4	5	
FSH	19.3	38.7	30.7	39.2	40.2	39.2	47.6	1.0-10.0 U/L
LH	7.2	18.9	14.2	15.6	19.7	20.9	19.2	2.0-12.0 U/L
Testosterone	11.2	13.6	14.8	16.1	14.7	12.5	14.5	9.5-28.0 nmol/L
IGF-1	16.0	41	41	40	16	30	31	11.0-29.0 nmol/L

Abbreviation: FSH, follicle-stimulating hormone; IGF-1, insulin-like growth factor 1; LH, luteinizing hormone.

**FIGURE 4** Five years postoperative pituitary MRI showing a 10 mm tumor on the right side

There are reports of white and gray matter volume reduction in KS patients. One study examining 65 KS subjects and 65 controls found those with KS had significantly smaller total brain volume (TBV), total gray matter volume (GMV), and total white matter volume (WMV) compared to controls.⁷ Interestingly, there were no differences in TBV, GMV, WMV, or cerebrospinal fluid (CSF) volumes between testosterone-treated KS (T-KS) and untreated KS (U-KS) patients,⁷ suggesting that the change is most likely a gene dosage effect. The reduction in brain volumes has been described in the caudate nucleus, putamen, temporal and frontal lobes, hippocampus, parahippocampus, and the amygdala. The reduction in TBV, GMV, and WMV as reported above was seen in our patient in addition to extensive periventricular white matter changes.

There are a few case reports in pediatric populations where children with KS were noted to have periventricular and subcortical white matter changes and learning disabilities.² There is a paucity of literature on the prevalence of periventricular white matter changes in the adult KS population. One case report describes a 56-year-old man with KS, with periventricular and subcortical white matter changes on

MRI and clinical manifestations of cognitive impairment.⁸ Vascular risk factors were not mentioned, and there were no reversible causes of cognitive dysfunction found. Our patient, with similar white matter changes, had minimal vascular risk factors, a negative leukodystrophy and vasculitis screen, and in contrast had no clinical manifestations. He had been working for decades as a dental assistant; albeit formal IQ has not been performed. These radiological findings raise the importance of the need for monitoring KS patients for white matter changes, and we suggest that monitoring for and modification of vascular risk factors is warranted.

Development of VTE and the increased thrombotic tendency in patients with KS.

KS patients are considered to have a genetically hypercoagulable state, with clinical implications for prevention, diagnosis, and management of VTE risk.⁹ The reported prothrombotic incidence is similar to that of inherited thrombophilias.^{3,10} The exact mechanism is unclear and is likely multifactorial. This may include X-linked gene dosage thereby resulting in genetic susceptibility, increased risk with reduced fibrinolytic activity, which has been associated with hypogonadism via increased levels of plasminogen activator—1 along with an increased incidence of metabolic syndrome in KS, which increases VTE risk.^{3,10} This was hypothesized in a large Swedish cohort study¹¹ of 3518 KS patients, followed over 40 years to assess their mortality. KS patients appeared to have a significantly raised mortality from pulmonary embolism with a standardized mortality ratio of 5.8.

In addition to KS, our patient was found to have a heterozygous mutation in factor V Leiden gene, unknown during initial consultations, likely having increased his risk for VTE. There is a need to consider screening and prevention of VTE in these patients, similar to patients with Cushing's disease. It has been suggested that KS patients should be routinely evaluated for genetic thrombophilia because they are at increased risk for thromboembolic phenomena, due to hormonal imbalance, and the presence of one or more genetic thrombophilia is likely to confer a significantly greater risk for VTE.¹⁰ However, in the absence of a clinical thromboembolic episode, it is unclear whether the presence of one

or more genetic thrombophilia would warrant therapy for VTE prophylaxis. This would have to be weighed against the potential adverse effects of anticoagulants. There is a need for risk stratification of VTE in KS patients with genetic thrombophilia.

7 | CONCLUSION

Klinefelter syndrome is often a delayed diagnosis, which can have important implications of poor quality of life and increased long-term metabolic and vascular complications. Early recognition of KS and monitoring and modification of vascular risk factors is important to improve overall morbidity and mortality.¹² Gonadotropinomas are generally considered nonfunctional; however, in the setting of a coexisting genetic androgen deficiency state, it is clinically relevant given that the increased gonadotropin secretion from the gonadotropinoma may potentially be raising endogenous levels of testosterone. Klinefelter syndrome is a prothrombotic state with potential life-threatening implications of VTE, and hence, it is important to screen for other compounding risk factors such as an inherited thrombophilia which raises the thrombotic risk further.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTION

DN: compiled the case report, performed literature search, and authored the manuscript; HN: revised the manuscript and contributed to literature search and content of the manuscript; AZ: initiated the first draft of this case report and contributed to literature search and content of the manuscript; JM and AD: revised and proofread the manuscript; BC: was an endocrinologist principally responsible for the care of the patient, initiated the preparation of this case report for scientific publication, reviewed and proofread and the final manuscript; VP: looked after patient in clinic, lead for write up, reviewed, and contributed substantially to the final version of this manuscript; all authors were directly or indirectly involved in the care of this patient.

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