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Achard-Thiers syndrome in post-menopausal women: The hidden complexity

Shivani Sureshchandra Thaker [1], Srija Reddy Kesireddy [2,*], Kavya Ammineni [3], Gul-E-Zernab [4], Rida Asghar [5], Srijamya [6] and Munawar Izhar [7]

[1] *Department of Medicine, Odessa national medical university, Ukraine.*
[2] *Department of Medicine, S.V.S Medical college, Telangana, India.*
[3] *Department of Medicine, PES institute of medical sciences and research, Kuppam, Andhra Pradesh, India.*
[4] *Department of Medicine, Benazir Bhutto Shaheed Medical college, Mirpur, AJK, Pakistan.*
[5] *Department of Medicine, Lahore medical and dental college, Pakistan.*
[6] *Department of Medicine, Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia.*
[7] *Department of Medicine, The University of Chicago Hospitals and Health System, Chicago, IL, USA.*

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Abstract

ATS, a rare disorder primarily affecting postmenopausal women, is characterized by the coexistence of DM Type 2 and elevated androgen levels. Despite its rarity, the syndrome poses diagnostic challenges due to its masked presentation under the guise of DM Type 2 and cosmetologic uses.

This study presents two unique cases of ATS, each with distinct onset scenarios, one following pregnancy and the other post-surgical transfusion. Both cases exhibit common symptoms of hirsutism and clitoromegaly, further emphasizing the importance of prompt and accurate diagnosis.

Laboratory, imaging, and clinical assessments play pivotal roles in identifying ATS amidst overlapping symptoms. Treatment options include hormone replacement therapy, antiandrogen therapy, glucose management, and cosmetic procedures. These cases show how important it is to have high clinical suspicion and a full evaluation to make sure that ATS is quickly identified and effectively treated in postmenopausal women who also have DM Type 2.

Keywords: Achard-Thiers syndrome; Insulin resistance; Type 2 Diabetes mellitus; Hyperandrogenism; Post menopausal women

1. Introduction

Achard-Thiers Syndrome (ATS), also known as diabetic-bearded woman syndrome, is a rare condition primarily affecting menopausal women. It is characterized by a combination of Type 2 Diabetes Mellitus (DM Type 2) and Cushing Syndrome [1]. This disorder manifests with hirsutism, virilism, and insulin resistance, with genetic factors playing a role in its development. Intriguingly, approximately half of women diagnosed with Polycystic Ovary Syndrome (PCOS) at an early age, have a higher risk of developing ATS after menopause.

This disorder is characterized by an excess production of androgens leading to abnormal hair growth in areas typically associated with males, such as the face, chest, abdomen, and back, along with clitoral enlargement, irregular menstrual cycles during reproductive phase, obesity, acne, and virilization [1]. Moreover, there are elevated blood glucose levels, resulting in typical symptoms of DM Type 2. Additionally, affected women may develop acanthosis nigricans,

* Corresponding author: Srija Reddy Kesireddy

hypertension, and osteoporosis, complicating the diagnosis of ATS. Furthermore, the presence of insulin resistance can lead to an increased risk of cardiovascular disease.

Managing ATS poses challenges, particularly due to its overlap with DM Type 2. Initial treatment primarily focuses on symptomatic management of diabetes, incorporating dietary modifications and, if necessary, insulin or medication [1]. A timely diagnosis allows for hormone replacement therapy, which is beneficial for women with ATS. Additionally, antiandrogen medications may be prescribed to regulate hormonal imbalances and alleviate associated symptoms.

Here, we present two rare cases of ATS with complex presentations and treatment approaches, highlighting the challenges of diagnosing and managing this syndrome.

2. Case 1 : ATS hidden under post-surgical transfusion complications

A 54-year-old woman presented to the clinic reporting excessive hair growth on her face and chest, as well as clitoral enlargement. Her medical history included a laparotomy and omental repair for a perforated peptic ulcer six months prior. After the surgery, she underwent blood transfusions, leading to rapid and widespread hair growth, particularly on her face, chest, and back. Initially attributed to the transfusions and expected to resolve within a month, these symptoms persisted and worsened over six months, accompanied by masculinization signs like voice deepening, increased muscle mass, and a significant weight gain of 40 pounds.

Laboratory tests were ordered and indicated normal testosterone levels but elevated DHEA and DHEA-S levels. Additionally, a high HbA1c level of 8.9% prompted insulin therapy initiation along with the Metformin and Semaglutide. Thyroid function tests yielded normal results, ruling out thyroid-related disorders, and urinalysis was negative for urinary infections. The initial differential diagnosis considered both pituitary adenoma and adrenal disorders, prompting a subsequent MRI of the brain, which excluded pituitary adenoma and confirmed adrenal gland pathology. Additionally, an inadequate suppression of 1 mg of overnight Dexamethasone along with an increased ACTH test confirmed the adrenal involvement. Further evaluation of gonadotropin levels, specifically LH and FSH, fell within normal limits, further supporting the adrenal diagnosis. Patient's report with the test results is shown in Table 1.

Table 1 Patient's laboratory reports

Tests	Patient's results	Normal Range
Fasting Blood Glucose	158 mg/dL	70-110 mg/dL
HbA1c Test	8.9%	<5.7%
Follicle-Stimulating Hormone (FSH)	86 mIU/mL	40-250 mIU/mL
Luteinizing Hormone (LH)	129 mIU/mL	30 - 200 mIU/mL
Thyroid-Stimulating Hormone (TSH)	2.8 mIU/L	0.4 - 4.0 mIU/L
Free T4	1.2 ng/dL	0.9 - 1.7 ng/dL
Testosterone	30 ng/dL	8 - 60 ng/dL
DHEAS (Dehydroepiandrosterone Sulfate)	450 µg/dL	26-200 µg/dL
Estradiol (E2)	10 pg/mL	0 - 20 pg/mL

To address her symptoms, the patient was initiated on Hormone Replacement Therapy (HRT) containing 50 mcg of Estradiol and 0.5 mg of Norethindrone to reduce androgen levels and the risk of osteoporosis. The regular assessments included blood pressure and lipid profiles. Prophylactic evaluations for thromboembolic events were also integrated into the follow-up regimen, utilizing D-dimer assays and Doppler ultrasound imaging to detect any signs of venous thrombosis.

In addition, the patient was prescribed Spironolactone at a dose of 150 mg daily for hirsutism. The potential side effects, particularly headache, dizziness, nausea, and alterations in potassium levels, were thoroughly communicated to the patient. As a result, regular potassium monitoring and renal function tests were necessary to prevent any renal problems. The backup plan of adrenalectomy was discussed with the patient in case of collapsed pharmacological intervention. However, the patient demonstrated marked clinical improvement within a month of initiating therapy,

which postponed any surgical considerations. Treatment plans include continuous monitoring of the treatment's long-term efficacy and side effects, with adjustments as needed based on the patient's ongoing response and health status.

3. Case 2: ATS hidden under post pregnancy complications

A 53-year-old female, post-menopausal, presented to the clinic with complaints of gradual onset of enlarged clitoris, thick hair growth on the face and body, and an increased frequency of migraines (2–3 episodes per week). She experienced similar symptoms of clitoromegaly, gradual weight gain, irregular menstruation, and hair growth on her face and body six months after giving birth at the age of 33. Her past medical history includes congenital hypothyroidism, chronic migraine, obesity, DM Type 2, and anxiety. She has a family history of DM Type 2 in her father. She is a homemaker and consumes a mixed diet with a good appetite, but she complains about constipation multiple times a week. She leads a sedentary lifestyle and has slightly disturbed sleep. Her medications include Levothyroxine, Alprazolam, and Sumatriptan as needed.

The patient's laboratory results indicated an elevated level of dehydroepiandrosterone sulfate (DHEA-S) at 483 ng/dl (reference range: 63-470 ng/dl) and serum testosterone at 88 ng/dl (reference range: 6.0-86 ng/dl). Additionally, the patient's HbA1c level was significantly elevated at 8%, indicating poor glycemic control (reference range: 5.7%-6.4%). MRI of the brain ruled out the presence of a prolactinoma.

Tablet Levothyroxine 75mcg was changed to 100 mcg per oral once a day was prescribed in the first visit hoping that as a potential cause of her symptoms. However, the patient noticed persistence of symptoms. Subsequently, 2-3 years later, she was diagnosed with DM type 2 and started on tablet Metformin 500mg per oral twice a day. The patient's visits and events are summarized in table 2.

Table 2 Events during Patient's clinic visit

	1st Visit (Post partum)	**2nd Visit**	**3rd Visit**
Age (years)	33	40	53
Weight(lbs)	158	195	180
BMI	27.1	33.5	30.9
Chief complaints	Weight gain over 6 months Painless swelling in the genital area Irregular menstrual cycles, excessive hair growth on body and face.	Fatigue, weight gain, increased appetite Nausea, mood swings, frequent urination at night Persistent swelling in the genital area Frequent migraine attacks (once a week).	Recurrence of facial and body hair Increasing swelling in the perineum Frequent migraine attacks (2-3 times a week) Extreme fatigue mild hoarseness of voice
Examination findings	Dry skin Coarse hair on the chin and thin hair on the body Genital examination: revealed clitoromegaly without any redness or discharge.	Dry skin Genital examination shows clitoromegaly without any redness or vaginal discharge	Dry skin Coarse hair is seen on face and body Genital examination reveals clitoromegaly
Lab results	Serum TSH: 10.2mU/L	Serum TSH: 3.9mU/L	Serum TSH: 3.3mU/L

	Fasting blood glucose: 93 mg/dl	Fasting blood glucose:130 mg/dl	Fasting blood glucose: 125 mg/dl
	2 hour Post meal glucose: 182 mg/dl	2 hour Post meal glucose:201 mg/dl	2 hour Post meal glucose: 190 mg/dl
	HbA1C: 6.1%	HbA1C:7.1%	HbA1C: 8%
	Complete urine examination: no significant findings	Complete urine examination: reveals presence of glucose.	Complete urine examination: no significant findings
			Dehydroepiandrosterone Sulfate(DHEA-S):483 ng/dl
			Serum Testosterone: 88ng/dl
Treatment	Tablet Levothyroxine 75 mcg per oral once daily	Tablet Metformin 500mg per oral twice a day Tablet Sumatriptan as per needed for migraine	Tablet Levothyroxine 100 mcg per oral once daily Tablet Spironolactone 100mg per oral once a day Tablet Metformin 500mg per oral twice a day Injection Erenumab subcutaneously once a month for migraine.

This case posed a challenge when the patient opted for laser hair removal after her 1st visit, making it difficult to detect abnormal hair growth on her 2nd visit thus hindering the earlier diagnosis. Even after temporary cessation of anti-anxiety pills and adopting wait and watch approach no changes were noticed. However, upon noticing the abnormal hair growth on her 3rd visit with increased frequency of migraines, clitoromegaly, hirsutism and past medical history of hypothyroidism and DM Type 2 raised the suspicion of hormonal imbalances prompting further investigations. Tablet Spironolactone (for hirsutism) and subcutaneous Injection Erenumab (for migraines) was started and symptoms were alleviated. This led to a conclusion that her symptoms stemmed from her increased androgen levels, prompting the recommendation to undergo Adrenalectomy for complete resolution of symptoms.

4. Discussion

ATS is a rare disorder that mainly affects postmenopausal women characterized by DM Type 2 and hyperandrogenism. ATS can be prevented by eating a healthy calorie and Fiber-rich diet, regular exercise, weight loss, and regular blood glucose monitoring [2]. Younger women with PCOS should be treated properly to reduce the risk of developing ATS in the future [2,3]. The pathophysiology of insulin resistance and hyperandrogenism in ATS is given in Figure 1. Hormone replacement therapy is recommended for postmenopausal women. Androgen excess can be treated with the help of antiandrogens. Adrenalectomy is helpful in uncontrollable androgen excess. Cosmetic measures such as waxing, and electrolysis can aid in excessive hair removal [2,3]. The treatment of ATS associated comorbidities is summarized in Table 3.

The two discussed cases present with differing clinical manifestations, yet share overlapping signs and symptoms with conditions such as Type 2 DM, and androgen-secreting tumors of adrenal or ovarian origin. Postpartum hormonal fluctuations and stress can also lead to androgen excess, heightening the risk for ATS. Cosmetic removal of excessive body hair, without recognizing the underlying syndrome, may obscure the diagnosis. PCOS, characterized by insulin resistance and hyperandrogenism during reproductive years, warrants attention as it can progress to ATS post-

menopause [5]. The combined impact of insulin resistance and hormonal imbalances exacerbates the risk of cardiovascular disease and osteoporosis [4].

Table 3 Treatment for ATS comorbidities

DM Type 2	Low calorie fiber rich diet, Regular exercise, weight loss for obese patients, Diabetes mellitus medications like Biguanides, SGLT-2 inhibitors, Sulphonylureas, Thiazolidinediones, DPP-4 inhibitors, GLP-1 receptor agonists or Insulin therapy, Regular blood glucose monitoring
Hyperandrogenism	Antiandrogens Adrenalectomy in case of uncontrollable hyperandrogenism
Excessive hair	Cosmetic measures like waxing, electrolysis

Many women tend to neglect these symptoms, resulting in a lack of further treatment. It is imperative that women with ATS are treated with HRT. However, due to the associated risks of thromboembolism consistent monitoring is essential. This should include regular assessments of D-dimer assays, and Doppler ultrasound imaging as part of a comprehensive risk management strategy. Additionally, while using spironolactone for hyperandrogenism, regular monitoring of renal function tests and potassium levels is recommended.

Given the hereditary nature of PCOS and ATS, women with affected blood relatives should be vigilant in early detection [2]. The overlapping symptoms of ATS complicate its diagnosis and treatment, potentially increasing its future prevalence. Consequently, opportunities for prevention may be missed, highlighting the need for heightened awareness and proactive management of these conditions.

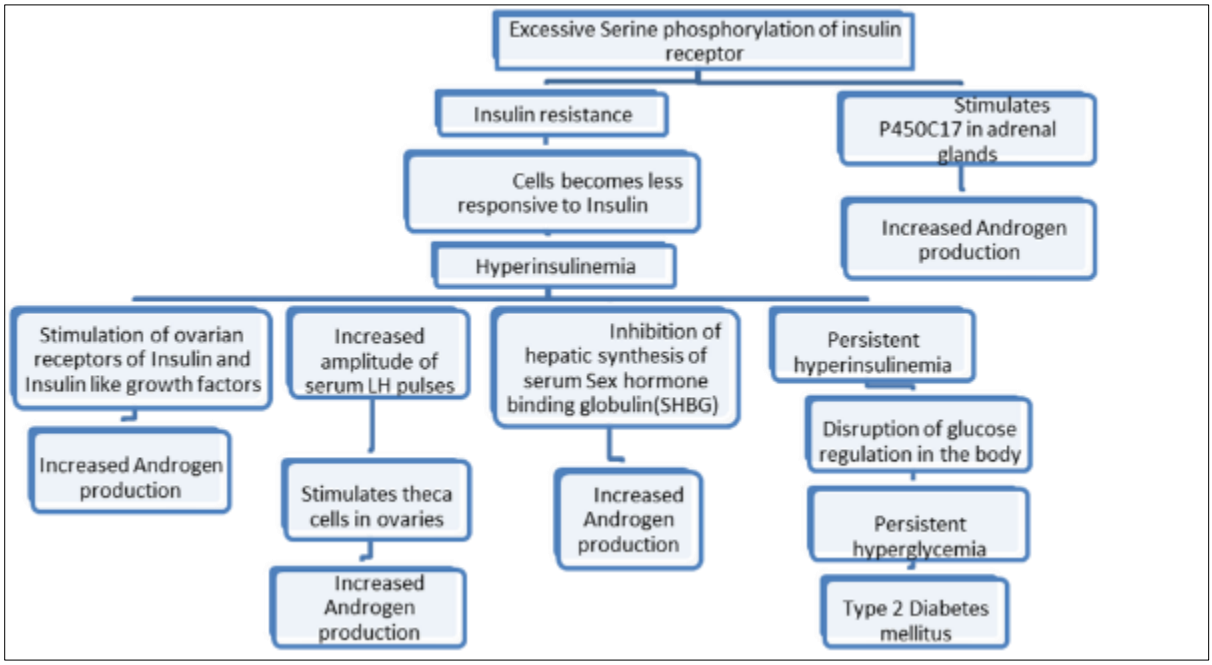

Figure 1 Pathophysiology of Insulin resistance and Hyperandrogenism in ATS

5. Results

The study presents the rare case of two postmenopausal women presented with DM type 2 and virilization symptoms, characteristic of ATS. Diagnosis in these cases was challenging due to overlapping features with other hyperandrogenic

conditions, such as Cushing's syndrome, adrenal tumors, and androgen-secreting ovarian tumors. Both patients exhibited clitoromegaly and hirsutism, critical indicators that prompted further investigation.

Comprehensive differential diagnosis was achieved through a combination of imaging techniques, laboratory assessments, and detailed clinical evaluations. Findings revealed the necessity of distinguishing ATS from other endocrine disorders that present with similar symptoms.

Treatment strategies included standard glycemic control with diabetes medications and lifestyle modifications, alongside anti-androgen therapies for managing hirsutism. In both cases, additional measures such as laser hair removal and cosmetic procedures were advised to address virilization symptoms. Patients were informed about required adrenalectomy in case of inadequate response to pharmacological interventions.

These cases highlight the importance of a multidisciplinary approach in diagnosing and managing ATS. Regular monitoring and personalized treatment plans are vital for effective disease management and improving patient outcomes.

6. Conclusion

The presented cases highlight the diagnostic challenges of ATS in postmenopausal women, particularly due to its symptom overlap with other hyperandrogenic conditions and DM type 2. Critical indicators such as clitoromegaly and hirsutism facilitated the identification of ATS amidst a complex clinical landscape. Effective diagnosis relied on a thorough differential approach incorporating imaging, laboratory tests, and clinical evaluations.

Treatment success was achieved through a combination of glycemic control, anti-androgen therapies, and cosmetic procedures, with adrenalectomy as a necessary intervention in case of failed pharmacological intervention. These cases highlight the necessity of a multidisciplinary approach for accurate diagnosis and personalized treatment, emphasizing the importance of ongoing monitoring to optimize patient outcomes. This approach ensures that ATS, despite its rarity and complexity, can be effectively managed, enhancing the quality of life for affected individuals.

Compliance with ethical standards

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Disclosure of conflict of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Statement of ethical approval

The patients' consent was taken to publish this research work including their disease information. The ethical approval to publish the patient's information was taken from the hospital.

Statement of informed consent

Written consent has been obtained from each patient or subject after full explanation of the purpose and nature of all procedures used.

Author contribution statement

Shivani and Srija contributed significantly to the organization and writing of the research paper. Kavya and Zernab focused on patient's data collection and additional writing tasks. Rida, alongside Srijamya, played a key role in drafting and editing the manuscript.

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