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CASE REPORT

An Occult Androgen-Secreting Ovarian Tumour Revealed by NP-59 Scintigraphy: A Case Report

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INTRODUCTION

Androgen-secreting tumours constitute a rare but important cause of hyperandrogenism, the possibility of which needs to be considered and excluded in patients with postmenopausal, severe, or rapidly progressive hyperandrogenism. Conventional anatomical imaging may help localise the source of androgen hypersecretion but is occasionally inconclusive. We describe a postmenopausal Chinese female with severe hyperandrogenism whose initial investigations were unrevealing. Iodine-131 6-beta-iodomethyl-19-norcholesterol (NP-59) scintigraphy successfully localised an occult, small androgen-secreting ovarian steroid cell tumour that was resected with subsequent resolution of hyperandrogenism.

CASE REPORT

A 49-year-old Chinese female presented with a 2-year history of hirsutism. She had early menopause at the age of 41 years but medical history was otherwise unremarkable. Clinical examination revealed hirsutism, male-pattern alopecia and facial acnes, while breasts and external genitalia were normal. She was also found to be hypertensive with blood pressure measuring around 170/110 mmHg. Hormonal profile revealed markedly elevated testosterone level of up to 33.9 nmol/L, more than 13 times the upper limit of normal level (<2.6 nmol/L). The rest of the hormonal profile and tumour marker panel were unremarkable. Imaging investigations to localise any androgen-secreting tumour were performed.

Transvaginal ultrasonography visualised a uterus of 6-week size, but the ovaries were not clearly seen. Contrast-enhanced computed tomography of the abdomen and pelvis did not reveal any adrenal or adnexal lesions, but several enhancing uterine nodules up to 1.6 cm, thought to be fibroids, were seen. Further ^{18}F-fluorodeoxyglucose positron emission tomography was also negative.

A dexamethasone-suppressed NP-59 scintigraphy was subsequently performed with intravenous administration of 37 MBq of NP-59. To suppress physiological adrenal uptake, oral dexamethasone 1 mg was prescribed 4 times daily for 13 days, starting 7 days before NP-59 injection.

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Planar scintigraphic images of the abdomen and pelvis were acquired from day 3 to 7 post-injection. Additional single-photon emission computed tomography–computed tomography (SPECT-CT) images were acquired on days 4 and 7. A positive finding was indicated by early visualisation of focal NP-59 uptake before day 5. Planar scintigraphic images from day 3 showed suspicious focal pelvic NP-59 uptake which persisted until day 7 (Figure 1), and a right adnexal lesion with NP-59 uptake was confirmed on SPECT-CT (Figure 2).

The patient underwent bilateral salpingo-oophorectomy. During the operation, the right ovary was found to be enlarged with a 2-cm unilocular cyst containing chocolate material. Histological findings of the right ovary were consistent with the presence of a small steroid cell tumour with no malignant features. Following removal of the tumour, her serum testosterone level normalised with resolution of virilising features. She also became normotensive.

DISCUSSION

Hyperandrogenism may manifest clinically as hirsutism and virilisation. Hirsutism is defined as excessive terminal hair that appears in a male pattern in women such as on the chin, upper lip or abdomen. Virilisation includes clinical features of more significant androgen excess such as clitoromegaly, deepening of the voice or increasing muscularity.[1] Causes of hyperandrogenism can be non-tumourous, such as polycystic ovarian syndrome, congenital adrenal hyperplasia, ovarian hyperthecosis, obesity, endocrinopathies, or iatrogenic; such causes can also be tumourous, such as adrenal or ovarian tumours.[2] Androgen-secreting tumours constitute a rare (5.8%) cause of hyperandrogenism although they are relatively more prevalent in postmenopausal (21.4%) than premenopausal women (2.0%).[3]

A clinical diagnostic algorithm for investigation of hyperandrogenism commonly includes adrenal and/or ovarian imaging to exclude an androgen-secreting tumour, especially in case of onset after menopause, severe clinical and/or biochemical hyperandrogenism, rapid progression, or presence of virilisation. In particular, very high serum testosterone (>150-200 ng/dL) and dehydroepiandrosterone sulphate (>6000 ng/mL) levels favour an androgen-secreting tumour of ovarian or adrenal origin, respectively.[2]

Ultrasonography and/or magnetic resonance imaging (MRI) are recommended imaging modalities to identify ovarian tumours.[2] Nonetheless androgen-secreting ovarian tumours may be difficult to detect if they are small in size. A recent study reported that ultrasonography and MRI failed to detect four of 31 androgen-secreting ovarian tumours (12.9%), ranging from 0.7 to 1.5 cm.[4] Although CT and MRI are recommended for detection of adrenal tumours,[2] incidental adrenal masses are common and may occur in 3% to 7% of adults, most of which are benign non-functioning adenoma.[5] Combined ovarian and adrenal vein sampling may be considered if ultrasonography, CT and MRI have failed to localise the androgen-secreting tumours, although its application has not been proven to reliably alter management. The success rate for catheterisation of all four veins, i.e., bilateral adrenal and ovarian veins, has been reported to be only 27%; hence, this technically difficult procedure may be considered only in centres with expertise.[6] Successful identification of androgen-secreting tumours with ^{18}F-fluorodeoxyglucose positron emission tomography has been reported in only a few isolated cases.[7]

The application of NP-59 in functional imaging commenced in the mid-1970s.[8] Steroid hormone synthesis initiates with arrival of cholesterol in adrenocortical cells by low-density lipoprotein. Twenty percent of NP-59 is incorporated in low-density lipoprotein and deposited in adrenocortical cells by a specific receptor, which does not follow the metabolic process and thus concentrates in the adrenocortical cells. This allows scintigraphic localisation of the hypersecreting adrenal and ovarian tumours in primary hyperaldosteronism, Cushing's syndrome, and hyperandrogenism. Previous case studies demonstrated the usefulness of NP-59 scintigraphy in localising both tumourous and non-tumourous ovarian and adrenal sources of androgen excess.[9-11] Among the reported cases, unilateral uptake was seen in androgen-secreting ovarian and adrenal tumours, and bilateral ovarian or adrenal uptake was seen in ovarian hyperthecosis and congenital adrenal hyperplasia. Normal scintigraphy was seen in peripheral conversion and increased end-organ sensitivity, while absent uptake (i.e., loss of normal physiological uptake) was seen in adrenocortical carcinoma. The unique role of NP-59 scintigraphy in localising the site of androgen hypersecretion was highlighted in two of the reported cases of adrenal hyperandrogenism, where the incidental abnormalities show absence of uptake. One patient had an adrenal lipoid cell tumour detected on CT. The other had congenital adrenal hyperplasia with adrenal glands

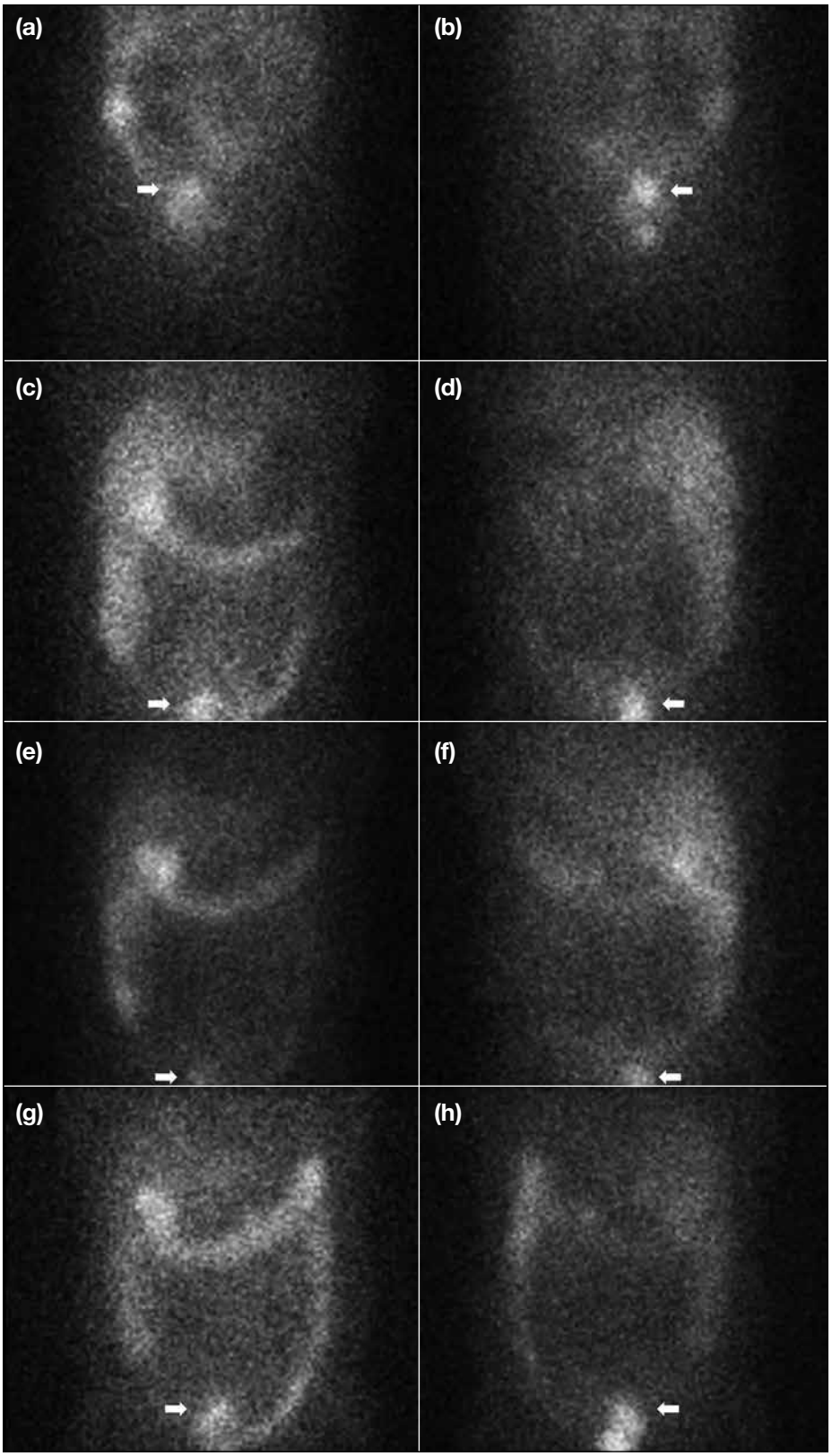

Figure 1. Iodine-131 6-beta-iodomethyl-19-norcholesterol (NP-59) scintigraphy with (a and b) day 3, (c and d) day 4, (e and f) day 5, and (g and h) day 7 anterior and posterior planar images of abdomen and pelvis. There was suboptimal coverage of the pelvis on day 5 images owing to initial assumption of pelvic activity (arrows) as physiological bowel activity. Day 3, 4 and 7 images raised the suspicion of possible abnormal focal increase in right adnexal NP-59 uptake (arrows), requiring additional single-photon emission computed tomography–computed tomography images for confirmation.

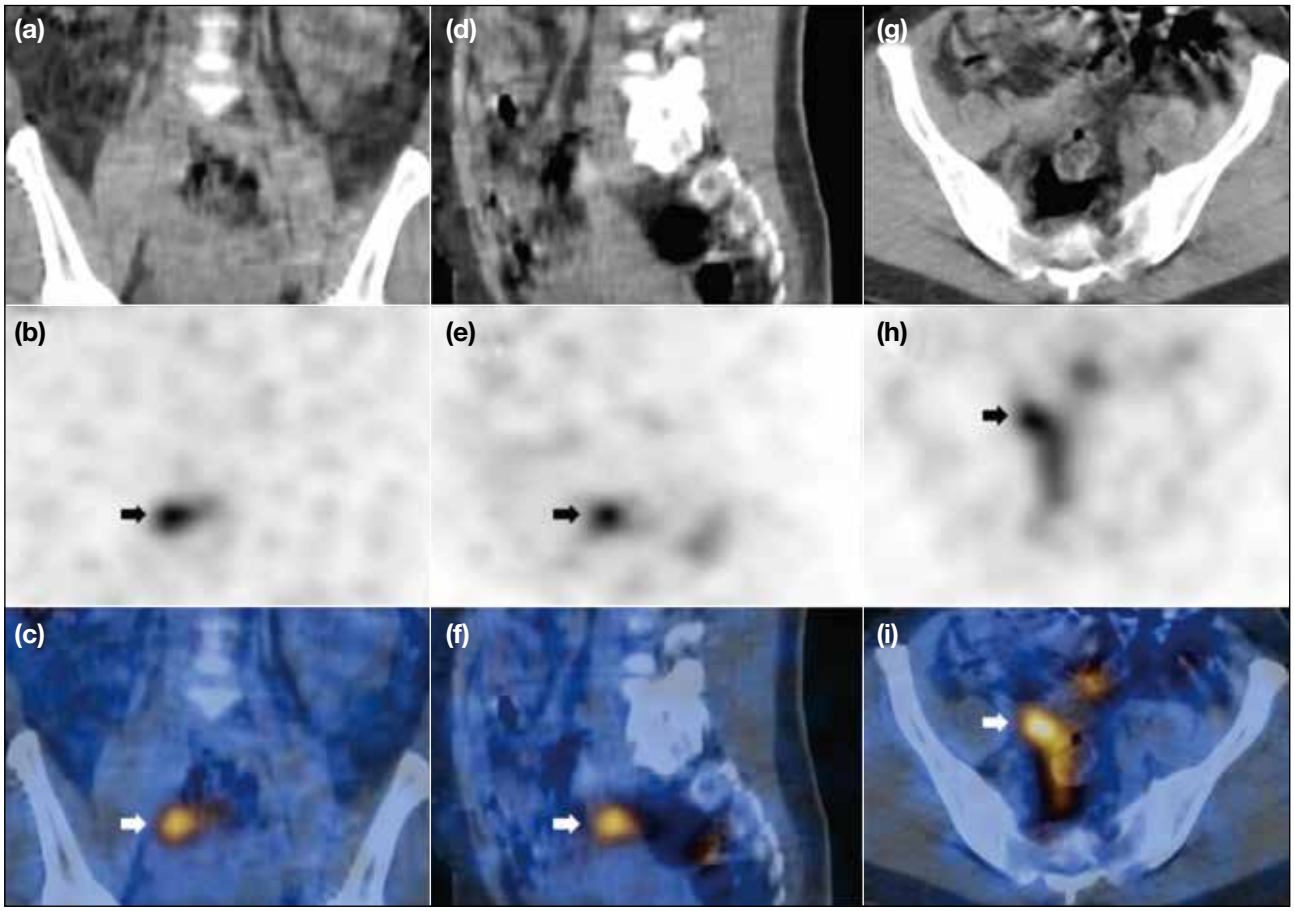

Figure 2. Iodine-131 6-beta-iodomethyl-19-norcholesterol (NP-59) scintigraphy with day 4 (a-c) coronal computed tomography (CT), single-photon emission computed tomography (SPECT) and fused SPECT-CT images, (d-f) sagittal CT, SPECT and fused SPECT-CT images, and (g-i) axial CT, SPECT and fused SPECT-CT images of pelvis. SPECT and fused images show an abnormal focal increase in NP-59 uptake at the right adnexal region (arrows) that could be distinguished from adjacent physiological large bowel activity.

appearing normal on CT. Both had incidental findings of ovarian masses, subsequently confirmed to be polycystic ovaries that were not contributory to the degree of hyperandrogenism. No false-positive NP-59 scintigraphic findings for hyperandrogenism have been reported in the English literature to date. Due to the rarity of this clinical condition, data on the diagnostic accuracy of NP-59 scintigraphy in hyperandrogenism are scarce.

As presence of intense physiological activity along the large bowel and its close proximity to androgen-secreting ovarian tumours hampers evaluation by NP-59 scintigraphy, preprocedural oral laxatives for bowel preparation have been recommended.[12] The availability of hybrid SPECT-CT technology, in addition to planar imaging, allows accurate delineation of any focal abnormal adnexal uptake from adjacent large bowel activity. The usefulness of SPECT-CT is well illustrated in this case where the focal abnormal adnexal uptake was difficult to appreciate on serial planar images but could be confirmed on SPECT-CT images.

There are several drawbacks to the widespread use of NP-59 scintigraphy in evaluation of hyperandrogenism. These include suboptimal image quality with iodine-131, relatively high radiation, prolonged imaging time, relatively high radiopharmaceutical cost, and potential adverse effects associated with use of high-dose dexamethasone as a pre-medication. Thus, NP-59 scintigraphy is often reserved for patients with clinical and biochemical evidence of ovarian or adrenal hypersecretion where conventional anatomical imaging has been unrevealing. A ^{18}F version of NP-59 is being developed for positron emission tomography imaging with promising initial data in imaging cholesterol trafficking and, specifically, uptake in adrenocortical

tissue.[13] It is expected that this ^{18}F version of NP-59 will become available for clinical use in the near future and provide higher image quality with lower radiation dose to help localise the site of hormone hypersecretion.

CONCLUSION

Accurate localisation of the source of androgen hypersecretion is critical to appropriate management in patients with suspected androgen-secreting tumours. This case report highlights the unique role of NP-59 scintigraphy in providing functional information and localising the site of androgen hypersecretion, which may not have been achievable by other non-invasive investigations. It is an indispensable and time-honoured nuclear medicine procedure that produces the most significant and conclusive results in such situations. Nevertheless the limitations of NP-59 scintigraphy limit its use to problem-solving rather than screening purposes. It is especially helpful in selected patients where there is a high suspicion of ovarian or adrenal hypersecretion but inconclusive conventional anatomical imaging.

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