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## Systemic lupus erythematosus with a non functioning pituitary macroadenoma

**Ummi Nadira, Rizna Abdul Cader, Norella C.T. Kong, Rozita Mohd, Halim A. Gafor**

Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia

### Summary

**Background:**

Malignancies are more common in patients with systemic lupus erythematosus (SLE) than the general population. SLE patients are recognized to have higher prolactin levels. However, there are very few reported cases of SLE with pituitary adenomas.

**Case Report:**

We report the second case of a pituitary adenoma in a patient with underlying SLE. A 51 year old lady presented with blurred vision and magnetic resonance imaging of the brain demonstrated a pituitary macroadenoma with mildly elevated serum prolactin levels. The diagnosis of a non functioning pituitary macroadenoma was confirmed histologically. The diagnosis of SLE was made on the basis of thrombocytopenia, antinuclear antibodies, anti double stranded DNA antibodies and lupus nephritis (confirmed on renal biopsy). The patient initially received medical therapy with carbegoline, followed by transsphenoidal neurosurgery for the pituitary macroadenoma. SLE with lupus nephritis was treated with steroids and low dose intravenous cyclophosphamide.

**Conclusions:**

Hyperprolactinaemia is prevalent in twenty to thirty percent of SLE patients but it is rarely due to a prolactinoma. The source of excessive circulating prolactin in SLE patients has not been fully determined.

**key words:**

**pituitary macroadenoma • systemic lupus erythematosus • prolactin**

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**Author's address:**

Rizna A. Cader, Nephrology Unit, Department of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latif, Bandar Tun Razak, Cheras, Kuala Lumpur, 56000, Malaysia, e-mail: rizna\_c@hotmail.com

## BACKGROUND

The association of systemic lupus erythematosus (SLE) with malignancies is more common than in the general population and its occurrence has been reported to be 3.2–11.4% [1,2]. SLE patients have an increased risk of certain types of cancer especially non-Hodgkin lymphoma, Hodgkin's lymphoma, lung and cervical cancers [1]. There is emerging evidence demonstrating a decreased risk of breast, ovarian and endometrial cancers in SLE [3]. Malignancies are among the leading causes of death in SLE patients [4]. The mechanism underlying the association between cancer and SLE remains largely unanswered. A potential link between cancer risk and drug exposure in SLE remains difficult to establish definitively because of the close association between disease activity and immunosuppression [5].

In general, prolactin-secreting adenomas or prolactinomas are the most common of all pituitary tumors [6]. Non-functioning pituitary adenomas represent approximately 30% of all pituitary tumors, are benign and are usually macroadenomas [6]. Patients with non functioning pituitary adenomas mainly present with symptoms due to the mass effect of the tumor and transphenoidal surgery is the treatment of choice.

Prolactin is a peptide hormone produced by the anterior pituitary gland that affects mammary gland growth and development. It is also produced at extra pituitary sites including lymph nodes. Prolactin is an important immunoregulator and up regulates the immune function, promoting autoimmunity. It has been speculated that prolactin may play a role in the pathogenesis of SLE [7]. SLE patients have been noted to have elevated prolactin levels but prolactinomas are extremely rare with only six case reports to date.

We present here a case of non-functioning pituitary macroadenoma in a patient with newly diagnosed active SLE. The non-functioning pituitary macroadenoma preceded the diagnosis of SLE. However, the patient had SLE manifestations for over two years and there was a delay in diagnosis as she had defaulted referral to the rheumatologist.

## CASE REPORT

A 51 year old lady with type two diabetes mellitus and hypertension presented in November 2010 with a three week history of right facial numbness and a one year history of blurred vision in the right eye. She denied any history of nausea, vomiting, headache, amenorrhoea or galactorrhoea. She was recently diagnosed at another hospital with a pituitary macroadenoma on magnetic resonance imaging (MRI) and referred to the neurosurgical team at our institution. Neurological examination revealed nystagmus, bitemporal hemianopia, reduced sensation of maxillary and mandibular distribution of the fifth cranial nerve and reduced hearing in the right ear. The rest of the central nervous system examination was normal. Whilst on the neurosurgical ward, she was referred for investigation of thrombocytopenia.

On reviewing her previous blood investigations, she was noted to have thrombocytopenia with a platelet count ranging from  $60\text{--}100 \times 10^9/\text{L}$  since 2007 but this was only picked up in 2009. This was initially attributed to ticlopidine but despite stopping this, her platelet count did not normalize. Full



**Figure 1.** Sagittal section of the MRI brain demonstrating the pituitary mass.

blood film demonstrated true thrombocytopenia with giant form platelets. Connective tissue screening in 2009 demonstrated the presence of anti nuclear antibody antibodies (ANA 1:640, homogenous pattern) but she defaulted follow-up. She had no bleeding tendencies and denied any joint pains, mouth ulcers, alopecia, photosensitivity or malar rash.

During this admission, the full blood count was normal except for thrombocytopenia ranging from  $59\text{--}90 \times 10^9/\text{L}$ . ESR was 63 mm/hr and C-reactive protein was 0.39 mg/dl (NR <0.5 mg/dl). Anti-double stranded DNA and ANA were positive (ANA 1: 640 homogenous pattern), C3 and C4 levels were 108 mg/dL (NR 79–152 mg/dL) and 22.7 mg/dL (NR 16–38 mg/dL) respectively. Urinalysis demonstrated blood 3+ and protein 2+. Urine protein creatinine index was 0.4 g/mmol (NR <0.02). Serum creatinine and albumin were 107  $\mu\text{mol/L}$  and 44 g/L respectively.

A diagnosis of SLE with haematological and renal involvement was made and she was treated with pulsed intravenous (IV) methylprednisolone followed by oral prednisolone and azathioprine. A repeat MRI demonstrated a large sellar mass with suprasellar extension, encasement of the intracavernous left internal carotid artery and compression of the optic chiasm (Figure 1). The hormonal studies were within normal limits except for an elevated serum prolactin level of 35.45  $\mu\text{g/L}$  (NR 1.39–24.20  $\mu\text{g/L}$ ). She denied any symptoms of hyperprolactinaemia and was diagnosed as having a non functioning pituitary macroadenoma. Neurosurgery was postponed until her platelet count increased and she was started on medical therapy with cabergoline in the interim.

In January 2011, she was reviewed at the SLE clinic and noted to have increasing proteinuria from 0.4 to 1.9 g/mmol despite being on immunosuppression. A renal biopsy showed focal lupus nephritis (WHO classification or ISN/RPS class III). She was treated with low dose intravenous cyclophosphamide 2 weekly for four doses and then monthly for 4 months. The prednisolone dose was tapered down to 10 mg daily and she remains on maintenance prednisolone with azathioprine and is in complete remission from her lupus nephritis. Her platelet counts normalized.

During this period, her neurological symptoms also improved and cranial nerve examination was normal. However, a repeat MRI brain in March 2011 showed no significant change in the size of the sellar mass despite carbegoline therapy. Surgical excision of the pituitary tumor was performed transphenoidally and histology confirmed a pituitary adenoma that was positive for growth hormone, prolactin, luteinizing hormone, follicular stimulating hormone and adrenocorticotrophic hormone.

## DISCUSSION

The mechanism underlying the association between cancer and SLE remains unanswered and the potential link between cancer risk and immunosuppressive drug exposure remains difficult to establish definitively. The predisposing factors include a genetic predisposition common to autoimmune and haematological malignancies, defects in the immune system that prevent tumour surveillance and a greater prevalence of conventional cancer risk factors in patients with SLE such as hormone replacement therapy use (although this was not the case in our patient) [8]. Exposure to immunosuppressive drugs also increases the risks of cancer in SLE [2]. However, it is unlikely to be related to the cumulative doses of immunosuppressive therapy as the highest risk of cancer occurs early in the course of SLE.

In this patient, the diagnosis of SLE was based on the presence of positive serology, haematological manifestation with thrombocytopenia and lupus nephritis. The diagnosis of a non functioning pituitary macroadenoma was made clinically, supported by the mildly elevated serum prolactin level and MRI findings. This patient was noted to have hyperprolactinaemia as the serum prolactin levels were above the normal range but not consistent with the diagnosis of prolactinoma.

Forty percent of pituitary adenomas cause hyperprolactinaemia. It has been reported that 20–30% of SLE patients have hyperprolactinaemia [9]. However, the source of excessive circulating prolactin in SLE patients has not been fully determined. Hyperprolactinaemia in a number of these patients may be secondary to medications, hypothyroidism or renal insufficiency. In most patients, the cause is not found and may be disease related. There are very few cases of SLE patients in whom the cause of the hyperprolactinemia is due to a prolactinoma [10,11].

Prolactin is an important immunoregulator and may play a role in the pathogenesis of SLE by stimulating immunoglobulin synthesis and autoantibody production [9]. *In vitro* studies have shown that prolactin increases production of anti-double stranded DNA antibodies and immunoglobulin by peripheral blood mononuclear cells in SLE patients [12].

Some studies have shown serum prolactin levels to correlate with disease activity [13] where as others have not [14]. The presence of high prolactin levels in many SLE patients without symptoms of prolactin excess and the lack of a clear cut correlation between serum prolactin levels and SLE disease activity may be due to the genetic differences among lupus patients. There is some evidence to suggest that among lupus patients, there may be a subset of patients with a genetic

susceptibility to the effects of hyperprolactinaemia. In our patient, the high prolactin level could be due to either disease activity or the non functioning pituitary adenoma. She was not on any medications that cause hyperprolactinaemia.

This patient was diagnosed with SLE only after the diagnosis of a non functioning pituitary macroadenoma. Therefore, a cumulative dose of cytotoxic therapy was not a risk factor. She was initially treated with steroids and azathioprine, but when the renal biopsy showed active lupus nephritis, a short course of intravenous cyclophosphamide was given. She was then maintained with azathioprine which is less carcinogenic.

## CONCLUSIONS

This is the first reported case of a rare association of a non functioning pituitary adenoma in patient with untreated SLE. A possible hypothesis for this association is the tumour was as a consequence of chronic inflammation or purely a coincidental occurrence. Further research is needed to establish the definite mechanisms.

## Take home message

SLE patients have hyperprolactinaemia but it is rarely due to a prolactinoma.

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