Case Report

New Onset Systemic Lupus Erythematosus with Pheochromocytoma

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ABSTRACT. We describe a patient with positive antinuclear and anti-Smith antibodies, proteinuria, and thrombocytopenia suggesting systemic lupus erythematosus (SLE). During hospitalization, the patient developed labile hypertension, tachycardia, and intermittent fever. A computer tomography scan of the abdomen showed an extraadrenal mass, which was confirmed as a pheochromocytoma. After removal of the pheochromocytoma, the patient's symptoms resolved and her serology normalized. Previous case reports describe SLE patients with adrenal pheochromocytomas that presented many years after the diagnosis of lupus. This is a novel case of pheochromocytoma discovered at the onset of SLE, with resolution of SLE manifestations shortly after its removal. (J Rheumatol 2002;29:1334–7)

Key Indexing Terms:
PHEOCHROMOCYTOMA SYSTEMIC LUPUS ERYTHEMATOSUS
CATECHOLAMINE HYPERTENSION ADRENOMEDULLIN

Two case reports[1,2] describe pheochromocytomas that were discovered many years after systemic lupus erythematosus (SLE) was diagnosed. We encountered a patient with atypical presentation of new onset SLE and concurrent manifestations of pheochromocytoma. After surgical resection of the tumor, blood pressure normalized and some autoantibodies diagnostic of SLE could no longer be identified on followup serologic analysis. Whether this association is an incidental finding remains to be elucidated.

CASE REPORT

A 39-year-old Filipino woman presented with a one week history of migratory polyarthralgia and fever. Her history was unremarkable. Autoantibody screening by her primary care physician revealed an antinuclear antibody (ANA) titer of 1:1280, homogeneous pattern. She was given prednisone 10 mg/day and subsequently was referred to Olive View-UCLA Medical Center for further care.

Upon hospitalization, initial examination showed a temperature of 39.6˚C, pulse 110 beats/min, blood pressure 127/78 mm Hg, and respiratory rate of 22. She had a grade III/VI apical systolic ejection murmur. Skin examination (and biopsy) showed a large congenital Becker's nevus covering most of her back, multiple café au lait spots over her trunk, and periungual hyperpigmentation of all fingers. Petechiae were noted over the soft palate. No malar or discoid rash was seen, nor evidence of active synovitis, muscle weakness, or neurological deficit.

Laboratory evaluation showed an elevated white blood cell count of 14,000/mm^3 (normal 3800–10,900/mm^3) with 93% neutrophils, hemoglobin 10 g/dl (11.2–16.0 g/dl) with mean corpuscular volume of 69 fl (80.3–98.1 fl), platelet count 169,000/mm^3 (130,000–400,000/mm^3), an elevated Westergren sedimentation rate of 64 mm/h (< 20 mm/h), blood urea nitrogen of 16 mg/dl (6–22 mg/dl), and creatinine of 1.0 mg/dl (0.6–1.3 mg/dl). Urinalysis showed 3+ protein, 11 red blood cells, and 1 white blood cell, with 24 h urine protein of 2.4 g/day. Blood and urine cultures showed no growth.

On Day 2 after admission, creatinine increased to 2.1 mg/dl. Then on Day 3, she developed severe acute respiratory distress, with chest radiograph showing diffuse bilateral lower lobe interstitial infiltrates, requiring transfer to the intensive care unit, emergent endotracheal intubation, and mechanical ventilation. Rheumatology consultation was obtained to evaluate for possible SLE. She was then empirically started on pulse methylprednisolone (1000 mg) for one day along with broad spectrum antibiotics for a presumptive diagnosis of SLE with acute lupus pneumonitis. Moreover, the creatine kinase (CK) was found to be elevated at 761 units/l with a positive troponin I of 50 (normal < 0.3). A bedside echocardiogram showed diffuse hypokinesis with an estimated ejection fraction of only 25%. A tentative diagnosis of lupus myocarditis was then also made.

During her stay in ICU, she developed severe thrombocytopenia with platelet count decreasing to 35,000/mm^3 despite platelet transfusions. Intravenous immunoglobulin therapy was then added to high dose corticosteroid therapy. She also developed acute hemolytic anemia with low haptoglobin, elevated LDH, and hyperbilirubinemia. Direct and indirect Coombs' tests were negative. Complement levels were low, with C3 51 mg/dl, C4 10 mg/dl, and CH50 < 25. Antibodies to Smith antigen, RNP, chromatin, and ds-DNA all tested strongly positive. The CK and aldolase

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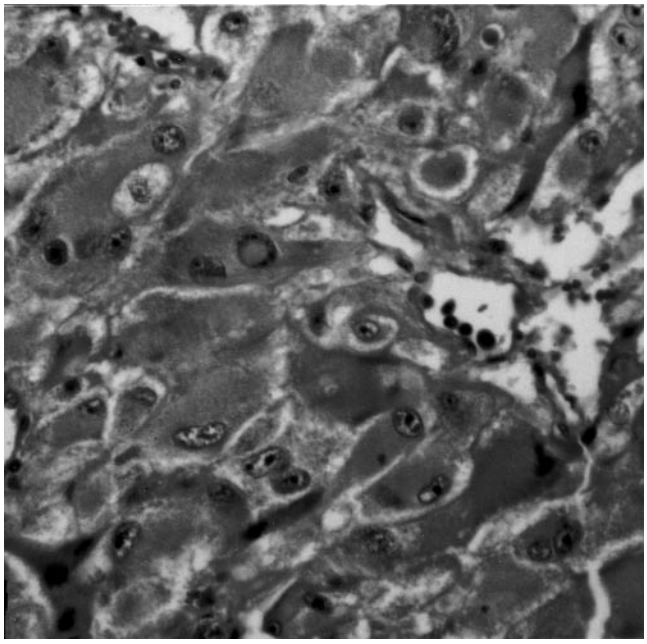
Submitted August 9, 2001; revision accepted December 17, 2001.

remained elevated, but she developed persistent proximal upper and lower extremity weakness. A deltoid muscle biopsy showed a neutrophilic vasculitis with fibrinoid necrosis of small arteriole walls and denervation grouped myofiber atrophy suggesting a vasculitis induced myositis (Figure 1B).

During hospitalization, her blood pressure was labile, spiking to 180–200/90–110 mm Hg, and was quite refractory to various antihypertensive medications. She also had episodes of tachycardia, with heart rates of 140–160 beats/min and temperatures to 41°C. A possible pheochromocytoma was then suspected as a cause for her labile hypertension and refractory tachycardia. A computer tomography scan of the abdomen showed a 5 cm heterogeneous left extraadrenal mass (Figure 2). A 24 h urine study showed an elevated urinary vanillylmandelic acid of 29.8 mg/24 h (normal 0–7) and metanephrine of 25,885 mg/24 h (30–350). Endocrine evaluation for conditions including multiple endocrine neoplasia (MEN) syndromes was unrevealing. Surgical consultation was requested; the left extraadrenal mass was then surgically resected after appropriate prior alpha-adrenergic receptor blockade, and the diagnosis of pheochromocytoma was confirmed on histologic examination (Figure 1A). After the resection, blood pressure and tachycardia gradually normalized. She continued to improve postoperatively and prednisone was tapered to 40 mg/day by discharge. With outpatient physical therapy, muscle strength and general condition gradually improved. By 4 months after hospital discharge, her prednisone dose was successfully tapered to 5 mg/day. Moreover, several of the previously positive autoantibodies became negative on repeat testing at 4 and 6 months after resection of the pheochromocytoma (Table 1).



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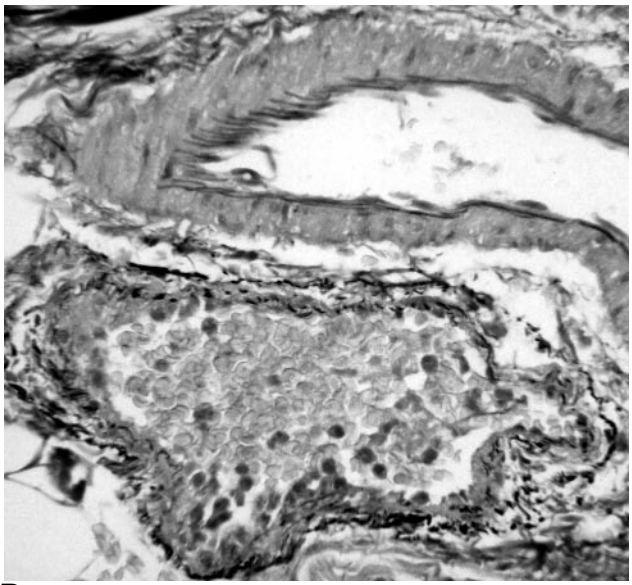

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Figure 1. A. Surgical removal of left extraadrenal mass showing nesting of tumor cells typical of pheochromocytoma; original magnification ×40. B. Biopsy of the deltoid muscle showing neutrophilic vasculitis of arterioles; original magnification ×40.

DISCUSSION

Several cases of pheochromocytomas in patients with rheumatic diseases have been reported[3-5], but only 2 in patients with SLE[1,2]. In both the previous cases, the pheochromocytoma developed many years after the diagnosis of SLE. Our patient, however, was newly diagnosed with both SLE and pheochromocytoma within 4 days of hospital admission. To our knowledge, this is a unique case of pheochromocytoma discovered at the onset of SLE, with partial resolution of SLE manifestations shortly after surgical removal.

The muscle biopsy to evaluate proximal weakness in our patient showed a striking presence of vasculitis, revealed as fibrinoid necrosis of small arteriole walls (Figure 1B). Vasculitis occurs in up to one-fourth of SLE cases, whereas only 3 case reports have documented vasculitis associated with pheochromocytoma[3-5]. Hypertension, however, is common in both SLE and pheochromocytoma[6-8]. Since our patient's blood pressure normalized shortly after surgery, her hypertension was likely to be due to the elevated catecholamines released from the tumor.

Pheochromocytomas are usually described as catecholamine-secreting tumors that arise from the adrenal medulla. However, about 10% are extraadrenal pheochromocytomas or catecholamine-secreting paragangliomas[8]. Pheochromocytomas are relatively uncommon neoplasms, occurring in 2 per 100,000 adults with peak incidence between 20 and 40 years of age, and they account for 0.1% of all cases of hypertension. The treatment of choice for pheochromocytomas is surgical resection[8].

Adrenomedullin is a potent vasodilatory peptide present in both normal adrenal medulla and pheochromocytoma[9]. Yudoh, *et al*[10] found a significant correlation between plasma adrenomedullin and tumor necrosis factor-alpha levels in patients with SLE. However, Meeran, *et al*[11] showed normal plasma adrenomedullin levels in patients with SLE. Therefore, its relevance to a possible relationship of pheochromocytoma and SLE remains to be determined.

An interesting observation was that several autoantibodies (Table 1) became negative by 4 months after surgical

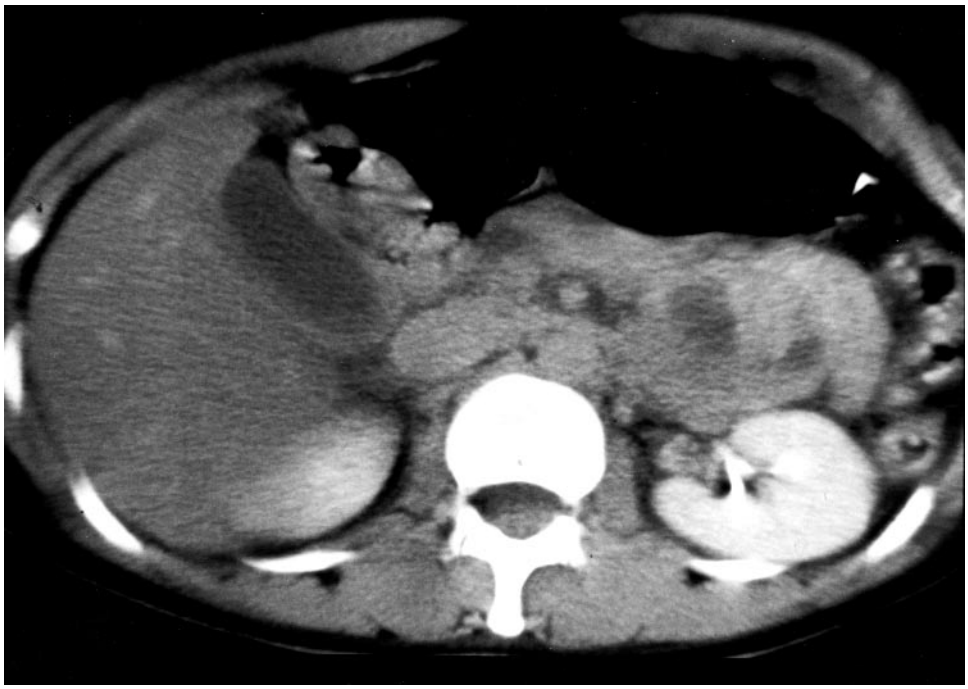

Figure 2. CT scan of the abdomen showing left extraadrenal mass.

Table 1. Serological test results* performed before and after resection of pheochromocytoma.

Laboratory Test (negative test value)	Before Resection	4 Months After	6 Months After
ANA titer (< 1:40)	1:1280	1:1280	1:1280
ANA pattern (none detected)	Speckled	Speckled	Speckled
Anti-Smith Ab (negative)	1:800	Negative	Negative
Antiribonucleoprotein Ab (negative)	1:1600	Negative	Negative
Anti-DNA Ab Farr assay (< 5.0 IU/ml)	16.8	26.3	27.5
Antichromatin Ab (negative)	Strongly +	Negative	Negative
Anticardiolipin Ab, IgG (< 15.0 GPL)	19.1	< 15.0	< 15.0
Anticardiolipin Ab, IgA (< 15.0 APL)	< 15.0	< 15.0	< 15.0
Anticardiolipin Ab, IgM (< 12.5 MPL)	< 12.5	< 12.5	< 12.5

* Laboratory testing was performed by the same laboratory for all tests.

resection of the pheochromocytoma, suggesting a possible causal relationship. This observation is supported by the study of Colburn, *et al*[12] suggesting that elevated serum catecholamines may stimulate the ß-adrenergic receptors of the B lymphocyte to produce antibodies that might be implicated in end-organ damage in SLE. Elenkov, *et al*[13] also suggested the role of norepinephrine in neuromodulation of lymphoid organs. Catecholamines (e.g., norepinephrine and epinephrine) may selectively downregulate the Th-1 response and shift toward Th-2 responses with dominance of humoral immunity.

That our patient's illness and laboratory abnormalities partially resolved after resection of the pheochromocytoma while her ANA and anti-ds-DNA antibodies continued to remain positive suggests that her SLE may have been accentuated by the pheochromocytoma. However, the high dose steroid treatment that she received may also have contributed to the remarkable postoperative improvement of her SLE. The association of pheochromocytoma and SLE in this report further emphasizes the need to consider when hypertension typically presumed secondary to SLE might actually have an underlying etiology other than SLE. Alternative etiologies for certain manifestations should be suspected especially in SLE patients with "atypical" clinical presentations. Finally, more research is needed in understanding the etiopathogenesis of SLE and how pheochromocytomas can influence SLE through neuroendocrine mechanisms contributing to autoimmunity[14,15].

ACKNOWLEDGMENT

The authors thank Judah White for manuscript assistance, Judith Harker for editorial assistance, and Dr. Bevra Hahn, Dr. Stanley Marcus and Dr. Richard Weisbart for their expert review of this case report. We also thank Dr. Nora Ostrzega and Dr. Marcia Cornford for assistance in slide photograph preparation.

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