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Commentary: The enigma of surgery to cure thymic paraneoplastic syndromes

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CENTRAL MESSAGE

A comprehensive review of 50 years of surgical reports helps clarify the degree of benefit of surgery in patients with thymoma and paraneoplastic syndromes.

Blalock and colleagues¹ began their 1939 landmark article on myasthenia gravis and tumors of the thymic region by quoting James Ewing: “No group of tumors has more successfully resisted attempts at interpretation and classification than those of the thymus.” In 1936, Blalock removed a thymic tumor in a 21 year-old woman who had a history of episodic exacerbations of myasthenia gravis. After the operation, she had improvement in her neurologic symptoms and required less medication. Interestingly, the patient was treated multiple times with radiation before the operation. This remarkable operation was undertaken because “it seemed possible that removal of the tumor might result in improvement, and because the risk inherent in the operative procedure was judged to be not great.”¹ Ironically, by 1939, only 4 cases of thymectomy to treat myasthenia gravis (in the setting of an associated thymoma) were known to Blalock and colleagues. These operations were performed by Sauerbruch, with 2 of the patients dying of subsequent mediastinitis and the remaining 2 patients, who survived the operation, noted to have improvement in their symptoms.¹ The concept of thymectomy for myasthenia gravis was soon extended by Blalock to patients *without* thymoma. The rationale for this leap of logic remains unclear.² In a 2-month period, weeks after joining Johns Hopkins University, Blalock proceeded to operate on 6 patients, with 1 death and improvement in the remaining patients.³ Among his first 20 patients, 4 died, 3 had no improvement, and 3 were described as essentially well with no need for prostigmine, a drug only identified and introduced into practice in the 1930s.⁴ Blalock was able to observe that the shorter the

duration of symptoms preoperatively, the greater the chance of favorable response to the operation.⁴ The operation was applied with variable results, and the benefits have been interpreted with skepticism in subsequent decades. From the initial work of Sauerbruch, it took more than a century before we obtained randomized prospective data demonstrating the benefit of thymectomy in patients with myasthenia gravis without thymoma, definitively establishing the role for surgery.⁵

In the spirit of Blalock, Zhao and colleagues⁶ present in this issue of the *Journal* a truly exhaustive review of a half century of reports on the topic of paraneoplastic syndromes in the setting of thymoma. Zhao and colleagues⁶ have reviewed more than 400 reports and summarized the surgical outcomes of more than 500 patients with this narrow inclusion criterion. In addition to myasthenia gravis, 123 paraneoplastic syndromes have been identified and associated with thymoma. Zhao and colleagues⁶ note that 76% of patients had improvement of paraneoplastic syndrome after thymectomy; unfortunately, however, 21% of this group have relapse occur. Patients with resolution of paraneoplastic syndrome had the best outcomes for long-term survival. Given the obscurity of some of these syndromes, we are unlikely ever to have quality data beyond the present article to guide therapy. Although surgery seems to have a role in the care of these patients,

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the immunologic basis of these paraneoplastic syndromes remains an enigma.

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Commentary: Toward a better understanding of the natural history of surgically treated thymoma associated with paraneoplastic syndromes

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Thymoma is a rare disorder, with an incidence of 0.15 cases per 100,000 person-years.¹ Surgery is the mainstay treatment for resectable tumors, with chemotherapy and radiotherapy offered in the neoadjuvant and adjuvant settings under certain circumstances.² Thymoma is associated with a host of autoimmune and nonautoimmune paraneoplastic syndromes (PNSs), the clinical implications of which have been studied mostly in the context of myasthenia gravis (MG). Notably, a randomized trial of surgical resection versus medical management alone for nonthymomatous MG demonstrated improved symptomatology and quality of life for complete thymectomy over medical management alone.³

In this issue of the *Journal*, Zhao and colleagues⁴ report the results of a systematic review of 407 published studies on paraneoplastic disorders in patients treated with surgery

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CENTRAL MESSAGE

Zhao et al provide an authoritative cataloging of paraneoplastic syndromes associated with surgically treated thymomas. Questions on long-term outcomes for syndromes other than myasthenia remain.

for thymoma between 1960 and 2019. They identified 507 patients, with a total of 123 distinct PNSs, which were present in 80% of patients before resection. Surgical resection led to remission or improvement of symptoms in 76% of patients. New onset of PNS was observed in 20% of previously asymptomatic patients, whereas recurrence of PNS occurred in 34% of patients, one third of whom had concurrent PNS and thymoma recurrence. A key finding was that complete resolution of PNS symptoms was associated with improved long-term survival.

This study is a noteworthy contribution to the literature. Compared with a recent study of PNSs in patients with thymoma from the International Thymic

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