Hong Kong College of Physicians

Case report for AIM Interim Assessment

Name of candidate (print and sign):
Hospital and Unit: **Specialty other than AIM:**
Name of supervisor (print and sign):
Date(s) and place (hospital) of patient encounter: 4/2020
Date of report submission: 10th March, 2021

Case report

Title: Stiff-person syndrome associated with thymoma

Case history:

A 59 years-old previously healthy male presented to our hospital with progressive episodic muscle spasms in bilateral lower extremities and trunk over one month. The symptoms were described as painful paroxysms which were exacerbated by startling sounds or percussion on the relevant muscles. Shortly afterwards, he developed restriction in mobility due to significant back muscle spasm which resulted in repeated falls during walking. One day prior to admission, he experienced acute low back pain in the absence of trauma. He denied any constitutional symptoms, there was no history of diabetes mellitus or family history of autoimmune diseases, malignancy or neurological disorders. Multiple trials of analgesics and muscle relaxants including paracetamol, tramadol, gabapentin, pregabalin, carbamazepine and clonazepam failed to relieve his symptoms.

Initial examination showed that patient was in agonizing pain. Neurological examination revealed generalized hypertonia and hyperreflexia over the bilateral lower limbs. Painful

tonic spasms were elicited by percussion on vastus medialis. There was no evidence of motor, sensory or coordination deficits. Cranial nerve examination did not demonstrate signs like ptosis, diplopia, dysphagia or fatiguability.

Computer tomography (CT) of the brain was unremarkable, X-Ray of the lumbar spine showed multiple fractures of T9, T10, L1 and L3 vertebral bodies. CT thorax illustrated a lobulated contrast-enhancing mass at anterior mediastinum measuring 5.7 cm x 3.5cm x 5.5 cm, which was closely abutting the surrounding mediastinal structures with extension to the retrosternal space, with high suspicion of a thymoma (Figure 1).

Complete blood count, liver and renal function tests were normal. Creatinine kinase level was 259 U/L (reference 39-308 U/L). Serum IgA, IgG and IgM level was normal with no paraprotein was detected. His fasting glucose level was 5.3mmol/l and HbA1c was 5.1%. Antibodies to glutamic acid decarboxylase (Anti- GAD65) antibodies test was strongly positive. Anti-acetylcholine receptor (AChR) antibody was < 0.20 nmol/L (reference < 0.46 nmol/L). His repetitive nerve stimulation test was not suggestive of neuromuscular junction disorder.

He was subsequently diagnosed with paraneoplastic stiff-person syndrome (SPS) by our neurology team. He was unresponsive to multiple lines of immunotherapy including intravenous immunoglobulin (IVIG), rituximab, intravenous methylprednisolone and plasma exchange. He eventually underwent thymectomy followed by post-operative adjuvant radiotherapy. Pathology of surgical specimen confirmed a WHO type B3 thymoma with invasion into lung parenchyma and pericardial tissue. Having completed a course of radiotherapy, his symptoms have gradually improved and regained functional capability.

Discussion and literature review

Our patient presented with progressive, episodic painful paroxysms of muscle spasms resulting in multiple vertebral fractures. Anti-GAD65 autoantibodies was strongly positive. Subsequent finding of thymoma by CT with resolution of stiffness after surgical thymectomy supported the diagnosis of thymoma related paraneoplastic stiff-person syndrome.

Stiff-person syndrome (SPS) is a rare neurological disorder characterized by progressive, episodic muscle spasm, stiffness and rigidity [1], [2] which can be disabling.

SPS has an estimated prevalence of one to two cases in a million worldwide, with a female predominance of which male to female ratio is 1:3. The exact pathophysiology of this disorder remains unclear, but many believed there is an autoimmunity component, such as evidence of high titre of anti-GAD65 autoantibodies [3], association with autoimmune disorders such as type 1 diabetes, Graves' disease and pernicious anemia. Although the pathogenic role of anti-GAD autoantibodies in SPS remains to be defined. It is postulated that the anti-GAD65 antibodies target on the gamma-aminobutyric acid (GABA) neurotransmitters at motor neuron pathway. Their anti-GABAnergic effect at the motor

nervous system trigger excessive excitation of muscle, resulting in debilitating muscle spasms and uncontrolled stiffness.

The disorder is further subdivided into three subtypes including classic SPS, partial SPS and paraneoplastic SPS.

Classic form of SPS usually presents with episodic muscle spasms over proximal lower limbs and lumbar area, and with time symptoms progress to the proximal part of upper limbs and truncal area. Muscle spasms are episodic and painful, and it can be forceful enough to cause gait disturbance, joint subluxation or even bone fracture. In our case, the forceful muscle spasms resulted in multiple levels of vertebral fractures, causing debilitating low back pain. Aggravation of symptoms is observed with tactile stimulation or emotional stress, which is known as startle reflex. Psychiatric involvement is common, including panic attack, phobia, depression and anxiety disorder. Autonomic dysfunction with tachycardia, tachypnea, diaphoresis or even fatal hypertensive spells has been described in patients with SPS.

Partial SPS is a focal form of the disease with isolated body parts involved, which is also known as Stiff-limb syndrome. Paraneoplastic SPS was described, with SPS associated with various malignancies including adenocarcinoma of breast, adenocarcinoma of lung, Hodgkin's lymphoma or thymoma [4], [5], Resection of the underlying tumour can result in resolution of symptoms. Our case demonstrated an example of paraneoplastic SPS secondary to underlying thymoma. A few case reports described the association of SPS with thymoma. Several cases were associated with myasthenia gravis, with muscle fatigability and detectable level of anti-AChR autoantibodies, which in our present case, myasthenia gravis was not evident from the clinical perspective, given a negative anti-AChR autoantibodies level.

Treatment of SPS includes symptomatic treatment and immunosuppressive therapy. Symptomatic treatment aims to alleviate the muscle spasticity, commonly used drugs include benzodiazepine and baclofen. However, a majority of patients with SPS had unsatisfactory response to isolated symptomatic therapy. Immunotherapy was shown to be effective in treatment of SPS, including intravenous immunoglobulin (IVIG) infusion, B cell depleting therapy such as rituximab [6], [7]. In cases refractory to IVIG or rituximab, plasma exchange can be considered as second line therapy [8]. However widespread use of plasma exchange is limited due to the procedural complexity and cost.

Glucocorticoid is another treatment option for patients with SPS. The treatment response can only be observed after prolonged course of high dose steroid, which could lead to multiple complications like osteoporotic fractures, hence this treatment option is no longer advocated nowadays.

For paraneoplastic subtype of SPS, surgical treatment of the underlying malignancy could result in symptoms improvement, even remission [9]. In our present case, multiple lines of immunosuppressive treatments were used including IVIG, rituximab, high dose pulse methylprednisolone as well as plasma exchange, none of the above treatments were successful in symptom control. Surgical thymectomy was the definitive answer in this scenario, which was also observed in other cases of paraneoplastic stiff-person syndrome with high degree of recovery.

Tables and figures:

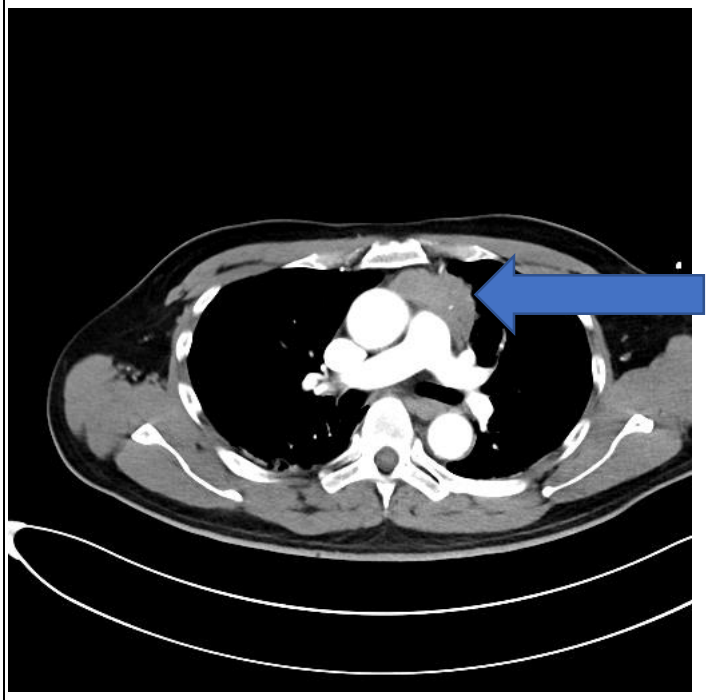

Figure 1.

Computer tomography scan showed a lobular thymoma (blue arrow) over anterior mediastinum.

Reference (not more than 10):

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No of words in Case History and Discussion (excluding references):_____1234_____

(should be between 1000-2000)

Declaration

I hereby declare that the case report submitted represents my own work and adheres to the prescribed format. I have been in clinical contact with the case selected. The case report has not been submitted to any assessment board or publication and it is NOT related to my second specialty(ies), if any. My consent is hereby given to the College to keep a copy of my case report, in written and/or electronic, at the College Secretariat and allow the public to have free access to the work for reference.

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(signature of Trainee)

Endorsed by Supervisor *

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(signature of Supervisor)