

Case report

Sequential appearance of ankylosing spondylitis, retroperitoneal fibrosis and achalasia: Coincidental association or evidence of autoimmunity?

P. Katsinelos, K. Christodoulou, I. Pilpilidis, A. Papagiannis, Maria Kalomenopoulou¹, Daphni Katsiba¹, A. Tarpagos, I. Katsos, N. Evgenidis²

SUMMARY

The association of idiopathic achalasia with ankylosing spondylitis and retroperitoneal fibrosis, to our knowledge not previously reported, is described in a 54 year old woman. We suggest that the consecutive occurrence of ankylosing spondylitis and retroperitoneal fibrosis, two well-known autoimmune disorders, before the presence of achalasia, reinforces the theory of autoimmunity in etiopathogenesis of achalasia.

Key words: Achalasia, Ankylosing spondylitis, Retroperitoneal fibrosis, Autoimmunity

INTRODUCTION

Achalasia is an acquired neurodegenerative disease of the esophagus, which causes an elective loss of inhibitory neurons in the ganglia of the enteric neural system of the upper gastrointestinal tract.¹

The disease occurs in a frequency of 7.9 cases per 100.000 people, is rare before the age of 25 years, but increases after the outbreak.² It usually occur in middle aged individuals and attacks both sexes nearly equally. The etiology of the disease is unknown. The existing data

support the familiar character of achalasia, the autoimmune or infectious etiology or that environmental factors intensify the occurrence of the disease.

We present a case of a 54 year-old woman, who over a period of 12 years presented ankylosing spondylitis, retroperitoneal fibrosis and achalasia. To the best of our knowledge this is the first description of this unusual combination.

CASE REPORT

A 54 year-old woman came to our department with an initial diagnosis of achalasia.

The patient complained of dysphagia when she consumed lipid and solid food, which had started one year earlier with a rapid recent deterioration. Her medical record showed back pain which appeared for the first time 12 years earlier, accompanied by morning stiffness at waking and stiffness in general after immobility. The diagnosis of ankylosing spondylitis was drawn based on the clinical report, x-ray and lab tests as well as the finding of a positive HLA-B27. The patient was treated with 3gr/day sulfasalazine and occasionally with nonsteroid anti-inflammatory drugs (NSAIDs) which resulted in an improvement her symptoms. Ten years later, the patient began experiencing malaise, abdominal and flank pain, anorexia, low-grade fever, and fatigue. She was evaluated by her local physician, who noted a mild anemia but no other abnormalities. Her systemic symptoms continued to worsen over the next month making her go once again to her physician. Repeated laboratory assessment revealed worsening anemia, Westergren erythrocyte sedimentation (ERS) of 110mm/h, and creatinine of 3.8mg/dl.

Department of Gastroenterology, Theagenion Hospital, Thessaloniki, Greece, ¹Department of Radiology, Central Hospital, Thessaloniki, ²Second Department of Internal Medicine, Aristotelion University, Ippokraton Hospital, Thessaloniki, Greece

Author for correspondence:

Panagiotis Katsinelos, 14 Marathonos str., 546 38 Thessaloniki, Greece

Abdominal CT scan revealed a periaortic mass extending laterally with obstruction of the ureters. Bilateral stent placement by cystoscopy was successfully completed, allowing adequate urinary drainage; however she continued to have systemic symptoms and an elevated ERS.

Retroperitoneal fibrosis (RF) was diagnosed, and because of her systemic symptoms and obstructed ureters, prednisone therapy was initiated at 1mg/kg/d. The patient responded quickly to prednisone therapy with resolution of her malaise and abdominal pain within 2 to 3 weeks. After 3 months of a prednisone taper to 10mg/d a renal furosemide (Lasix) scan revealed partial residual obstruction of both ureters. Repeat CT scan demonstrated shrinkage of the periaortic mass. Over the next 9 months, the patient's course was stable and for the last 2 years partial obstruction of both ureters has remained, and a small periaortic mass is visible by CT scan.

After admission to our department, physical examination, stool hemocult and laboratory tests including complete blood count, liver tests, creatinine, amylase, urinalysis and chest x-ray were normal. A barium esophagram showed a dilated esophagus with a smooth, tapered, conical narrowing of the distal segment.

Esophageal manometry showed aperistalsis of the esophageal body and failure of the lower esophageal sphincter to relax after deglutition. Esophagogastroduodenoscopy showed a dilated esophagus without peristalsis. The endoscope could be passed from esophagus to stomach with mild resistance, and the mucosae of these structures were normal.

The diagnosis of achalasia was made and the patient underwent pneumatic dilatation of the cardia with considerable immediate relief of her dysphagia. The patient's postprocedure course was unremarkable. At her last visit in February 2000 she was able to swallow all forms of food without distress.

DISCUSSION

Histocompatibility antigen HLA-B27 is a specific antigen which is thought to be associated or coupled with a corresponding immune response gene located in intimate proximity to chromosome 6. Some investigators speculate that these immune responses might be the agents provocateurs in the hypothetical pathogenesis of associated diseases, the histocompatibility antigens merely serving as passing markers.^{3,4}

Ankylosing spondylitis and retroperitoneal fibrosis

are two well-known autoimmune disorders. Of patients with known ankylosing spondylitis about 88%-97% show HLA-B27.⁵ A recent study relating to aetiopathogenesis of idiopathic retroperitoneal fibrosis showed the presence of immunophenotype HLA-B27 in 44% of cases and also revealed immunological profile and lymphocyte populations with typical features of chronic immune disease.⁶

Review of several studies and case reports indicates that there are several aetiologies for "idiopathic achalasia" such as familial,^{7,8} autoimmune,^{9,10} infectious,^{11,12} or environmental causes.²

Misiewicz et al suggested an autoimmune etiology when they noted round cell infiltration of ganglion cells only in specimens of mildly dilated distal esophageal achalasia. Monocytic infiltration of myenteric ganglion cells was also noted by Lendrum¹³ and Cassella and co-workers.¹⁴

In a study performed in the laboratory of the Walter Reed Army Medical Center, Wong et al¹⁵ found a connection between achalasia and a class II histocompatibility antigen DQw1, which could mean an autoimmune process. They formulated the theory that infection or a toxic inflammatory process causes the release of interferon gamma, consequently provoking an agent class II antigen expression on neural tissue. Recognising the particular antigen as foreign, the activated lymphocytes finally destroy neural tissue. This results in the development of an insidious process during which neuropathology could imitate a long-term degenerative neurologic disorder, initially combined with lymphocytic infiltration which finally results in replacement of the Schwann cells.

Supporting the hypothesis that an infection could cause an autoimmune process, Jones et al¹¹ performed a complement fixation test on¹⁸ achalasia patients and 12 age and sex-matched control subjects. They noted significantly higher antibody titers to the measles virus in achalasia patients as compared to control subjects. Likewise, Robertson et al¹² found a significant correlation between varicella-zoster complement fixation titers in 58 achalasia patients versus 40 control subjects. A subsequent landmark study¹⁶ utilizing DNA hybridization techniques to identify varicella-zoster in esophageal tissue revealed positive results in 3 of 9 achalasia specimens but negative results in 20 matched control subjects.

The consecutive occurrence of two well-known autoimmune disorders in our patient, before the presence of achalasia, reinforces the theory of autoimmunity in aetiopathogenesis of achalasia. We believe that the ex-

istence of histocompatibility antigen HLA-B27 caused an autoimmune process which consecutively, in a period of 12 years, attacked the joints the retroperitoneal space and the neural cells of the esophageal myenteric plexus.

REFERENCES

1. Wong RKH, Maydonovich CI: Achalasia, The Esophagus. Edited by DO Castell. New York, Little-Brown Company, 1992; pp 219-245.
2. Mayberry JF, Atkinson M. Studies of incidence and prevalence of achalasia in the Nottingham area. *Q J Med* 1985; 56:451-456.
3. McDevitt HO, Bodner WF. HLA, immune response genes and disease. *Lancet* 1974; 1:1269-1273.
4. Brewerton DA. HLA-B27 and the inheritance of susceptibility to rheumatic disease. *Arthritis Rheum* 1976; 19:656-662.
5. Brewerton DA, Caffrey M, Hart FD. Ankylosing spondylitis and HLA-B27. *Lancet* 1973; 1:904-907.
6. De Luca S, Terrone C, Manassero A, Rocca S, Rossetti S. Aetiopathogenesis and treatment of idiopathic retroperitoneal fibrosis. *Ann D' Urol* 1997; 32:153-159.
7. Kilpatrick ZM, Miller SS. Achalasia in mother and daughter. *Gastroenterology* 1972; 62:1042-1044.
8. Mackler D, Schneider R. Achalasia in father and son. *Dig Dis Sci* 1978; 23:1042-1045.
9. Misiewicz JJ, Wallerr SL, Anthony PP, Gummer JWP. Achalasia of the cardia: pharmacology and histopathology of isolated cardiac sphincteric muscle from patients with and without achalasia. *Q J M* 1969; 38:17-30.
10. Verne JE, Sallustion JE, Eaker EY. Anti-myenteric neuronal antibodies in patients with achalasia: a prospective study. *Gastroenterology* 1995; 108:A705.
11. Jones DB, Mayberry JF, Rhodes J, Munro J. Preliminary report of an association between measles virus and achalasia. *J Clin Pathol* 1983; 36:655-657.
12. Robertson CS, Martic BAB, Atkinson M. Possible role of herpes viruses in the etiology of achalasia of the cardia. *Gut* 1990; 30:A731.
13. Lendrum FC. Anatomic features of the cardia orifice of the stomach with special reference to cardiospasm. *Arch Intern Med* 1937; 59:474-478.
14. Cassella RR, Ellis FH, Brown AL. Achalasia of the esophagus: pathologic and etiologic considerations. *Ann Surg* 1964; 160:174-179.
15. Wong RKH, Maydonowitch CL. Significant DQw1 association in achalasia. *Dig Dis Sci* 1989; 34:349-353.
16. Robertson CS, Martin BAO, Atkinson M. Varicella-zoster virus DNA in the oesophageal myenteric plexus in achalasia. *Gut* 1993; 34:299-302.