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2017-2020

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AIM AND SCOPE

World Journal of Clinical Cases (*World J Clin Cases*, *WJCC*, online ISSN 2307-8960, DOI: 10.12998) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

The primary task of *WJCC* is to rapidly publish high-quality Autobiography, Case Report, Clinical Case Conference (Clinicopathological Conference), Clinical Management, Diagnostic Advances, Editorial, Field of Vision, Frontier, Medical Ethics, Original Articles, Clinical Practice, Meta-Analysis, Minireviews, Review, Therapeutics Advances, and Topic Highlight, in the fields of allergy, anesthesiology, cardiac medicine, clinical genetics, clinical neurology, critical care, dentistry, dermatology, emergency medicine, endocrinology, family medicine, gastroenterology and hepatology, geriatrics and gerontology, hematology, immunology, infectious diseases, internal medicine, obstetrics and gynecology, oncology, ophthalmology, orthopedics, otolaryngology, pathology, pediatrics, peripheral vascular disease, psychiatry, radiology, rehabilitation, respiratory medicine, rheumatology, surgery, toxicology, transplantation, and urology and nephrology.

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Prosthetic reconstruction of the trachea: A historical perspective

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Abstract

This review discusses the history of tracheal reconstruction;

from early work to future challenges. The focus is primarily on prosthetic tracheal reconstruction in the form of intraluminal stents, patch repairs, circumferential repairs and replacement of the trachea. A historical perspective of materials used such as foreign materials, autografts, allografts, xenografts and techniques, along with their advantages and disadvantages, is provided.

Key words: Tracheal stenosis; Trachea; Prostheses and implants; Stents

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Core tip: Reconstruction of tracheal defects has historically been difficult, predominantly due to the lack of an intrinsic blood supply. Direct anastomosis is generally considered to be the best option. For larger defects, stenting and prosthetic reconstruction remain the primary methodologies. In light of the recent scandal surrounding tracheal replacement, this article aims to give a historical review of tracheal reconstruction methods.

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INTRODUCTION

Tracheal reconstruction has been widely researched over the last 50 years. There are numerous indications for tracheal reconstruction, most frequently post-intubation injuries, idiopathic stenosis, neoplasia and re-stenosis following surgery^[1].

Following tracheal resection, primary reconstruction with direct anastomosis of the patient's own tracheo-bronchial tissue is generally accepted as the best

option^[2-7]. Anatomical studies suggest that up to half of the trachea can be resected in adults and directly anastomosed, without undue tension, by implementing mobilisation techniques such as suprahyoid release incisions and/or dissection of the hilum and pulmonary ligament^[8]. This has been corroborated in large studies, with acceptable safety profiles and good long-term results, although the limits vary depending upon the patient's age, body habitus, local anatomy, co-morbidities and previous treatments^[1,9-12].

In patients with very extensive pathology, direct anastomosis following resection is not possible and as such, either stenting or replacement with a prosthesis remain the two principle options. This provides a significant subset of patients. For example, long-segment defects (greater than 50% of the trachea) constitute approximately half of tracheal stenosis cases, although more recently this has been innovatively and successfully managed *via* a slide tracheoplasty procedure^[13,14]. A range of materials have been attempted and no ideal prosthesis has yet been developed. The ideal prosthesis is airtight, of adequate consistency to prevent collapse, well accepted by the host thus causing minimal inflammatory reaction, impervious to fibroblastic and bacterial invasion of the lumen and allows ingrowth of respiratory epithelium along the lumen^[15,16].

In this review article we will provide a historical overview of tracheal reconstructive trends.

EARLY WORK

In the late 1890s and into the twentieth century, interest in tracheal reconstruction evolved^[17-20]. Initially, as with many surgical specialties, a knowledge base was formed principally through isolated case reports. The focus at this time was autogenous replacements such as skin alone, or skin and fascial grafts^[21,22]. Daniel *et al.*^[23] heralded the advent of a more scientific approach with experimental animal studies. Throughout this period there was a transition from autogenous materials to solid prostheses such as tantalum, polyethylene, acrylic and steel tubes^[24-27]. No ideal prosthesis was found and outcomes were variable. Indeed, often composite approaches were taken, usually in the form of a solid prosthesis with fascia lata grafts. The level of evidence remained low.

1950s TO THE POROUS PROSTHESIS

Following this initial interest and *in vivo* work (Table 1), Gebauer was amongst the first to develop porous prostheses to counteract some of the drawbacks of solid prostheses^[28,29]. It was found that a porous prosthesis more closely approximates the function of tracheal cartilages as compared to a solid prosthesis^[30]. However complications including strictures, granulation formation, chronic infection, pressure necrosis from the prosthesis and dislodgement remained problematic. Erosion of

the brachiocephalic artery was also not infrequent. The porous structure was calculated to permit ingrowth of host connective tissue thus incorporating the prosthesis into the tracheal site; it was found that a minimal porosity of 40 to 60 μm is necessary for capillary ingrowth^[31]. There was a proliferation of literature and animal studies in this field during the 1950s and 1960s^[32-36]. This culminated in a better understanding of an ideal prosthesis in that the graft should be airtight, have adequate consistency, be well accepted by the host, cause minimal inflammatory reaction, be impervious to fibroblastic and bacterial invasion into the lumen but ideally allow ingrowth of respiratory epithelium along the lumen^[15,33,35]. The decision of material to trial was often dependent upon industrial and commercial advances and availability, ranging from steel wire, tantalum, marlex, PTFE, dacron and teflon^[2,29-36]. Combinations of materials were often employed. Towards the end of this period, as a result, prosthetic reconstruction of the trachea was being performed in human patients^[37,38]. The most promising outcomes were with Silicone prostheses. The Neville group pioneered this approach and developed the Neville prosthesis, a silicone based mould under high compression available as straight or bifurcated tubes^[15,16]. In this series of 62 patients, outcomes were reported to be good and the use of silicone was explicated by its resilience, non-reactivity, smooth inner surface and ability to be readily moulded^[15,39]. This, therefore, fulfilled all the criteria for an ideal graft except for ciliated epithelium traversing the inner surface. Suture line granulomas remained problematic and were treated endoscopically^[15,16,37]. This connective tissue ingrowth initially serves to fix and integrate the porous prostheses but this continued proliferation leads to scar tissue, obstruction and stenosis alongside with resultant chronic infection^[31].

At this time, progress was also being made in surgical techniques, led by Grillo's team in Boston. Anatomic studies indicated that up to half the trachea in adults can be resected and closed primarily with an end to end anastomosis^[8]. The same group has validated this with resulting large case series with low morbidity and mortality^[3,4,9-11,13,31]. Slide tracheoplasty and other mobilisation techniques including suprahyoid release incisions, dissection of the hilum and pulmonary ligament have all been successfully used to achieve primary closure. Undoubtedly this remains the gold standard management of tracheal resection. However, it is not always possible and is dependent upon the patient's age, body habitus, local anatomy, extent of disease, co-morbidities and previous treatments such as radiotherapy^[3,4,9-11,13,31].

These studies therefore established that primary repair remains the method of choice and should be employed wherever possible. In addition, it was concluded that an entirely satisfactory tracheal graft will never be available^[31,35]. The silicone airway is at least as satisfactory as any prosthesis yet fashioned for tracheal replacement and any alternative must be wholly dependable with minimal morbidity and mortality^[31]. This remains the

Table 1 Tracheal reconstruction methodology over time

Year	First author	Category ¹	Material	Study type (number)
1898	Bruns ^[17]		Prosthesis unknown	Human
1911	Hohmeier ^[18]	Autogenous	Fascia lata	Animal
1912	Levit ^[19]	Autogenous	Fascia	Human (1)
1927	Fairchild ^[20]	Autogenous	Skin	Human (1)
1935	LeJeune ^[21]	Autogenous	Split thickness skin graft	Human (2)
1945	Crafoord ^[22]	Autogenous	Cutaneous and costal cartilage	Human (1)
1946	Belsey ^[24]	Solid prosthesis	Steel with fascia lata	Human (1)
1948	Clagett ^[25]	Solid prosthesis	Polyethylene	Human (1)
1948	Daniel ^[23]	Solid prosthesis	Fascia, Metal Tube	Animal
1948	Longmire ^[26]	Solid prosthesis	Acrylic tube	Human (1)
1949	Rob ^[27]	Solid prosthesis	Tantalum with fascia lata	Human (4)
1949	Kergin	Autogenous	Pericardium and bronchus	Human (1)
1950	Jarvis	Solid prosthesis	Stainless Steel	Human (1)
1950	Gebauer ^[29]	Porous prosthesis	Wire-enforced dermal graft	Human (11)
1951	Bucher ^[30]	Porous prosthesis	Stainless steel wire mesh	Animal
1952	Cotton ^[2]	Solid prosthesis	Stainless steel tube	Human (2)
1953	Edgerton	Solid prosthesis	Split grafts with foam rubber	Human (12)
1953	Pressman ^[32]	Autogenous	Decalcified bone	Animal
1955	Morfit	Solid prosthesis	Polyethylene	Animal
1962	Beall ^[35]	Solid prosthesis	Polyethylene	Animal
1964	Aletras	Solid prosthesis	Teflon frame with pericardium	Animal
1967	Graziano ^[33]	Porous prosthesis	Silicon with dacron	Animal
1968	Pearson ^[34]	Porous prosthesis	Marlex (Polyethylene)	Animal
1973	Monk	Autogenous	Dermal grafts	Human (6)
1973	Demos	Porous prosthesis	Silicone	Animal
1974	Montgomery ^[38]	Porous prosthesis	Silicone t tube	Human (94)
1974	Pearson	Porous prosthesis	Marlex (Polyethylene)	Human (6)
1976	Neville ^[37]	Porous prosthesis	Silicone	Human (26)
1977	Lindholm	Autogenous	Bone/periosteum/muscle	Human (2)
1982	Neville ^[15]	Porous prosthesis	Neville prosthesis (silicon with dacron rings)	Human (54)
1982	Westaby	Porous prosthesis	Bifurcated silicone stent	Human (1)
1985	Toomes ^[6]	Porous prosthesis	Neville prosthesis (silicon with dacron rings)	Human (9)
1986	Scherer ^[67]	Tissue engineering	Bioprosthesis	Animal
1989	Har-El	Autogenous	Alloplast implanted muscle flap	Animal
1990	Neville ^[39]	Porous prosthesis	Silicone tubes	Human (62)
1990	Cull	Porous prosthesis	PTFE	Animal
1990	Jorge	Porous prosthesis	PTFE	Animal
1990	Kato ^[66]	Autogenous	Oesophagus and Silicone T tube	Animal
1990	Letang ^[65]	Homograft	Jejunum and Silicone T tube	Animal
1990	Varela	Porous prosthesis	Stainless steel wire mesh	Human (5)
1992	East ^[64]	Autogenous	Composite fascia, septum	Human (1)
1994	Okumura ^[63]	Porous prosthesis	Collagen and Marlex mesh	Animal
1996	Sharpe	Porous prosthesis	Marlex and pericardium	Human (1)
1996	Elliott ^[62]	Homograft	Homograft	Human (5)
1997	Kiriyama ^[61]	Homograft	Oesophageal autograft	Animal
1997	Teramachi ^[60]	Porous prosthesis	Marlex with collagen	Animal
2000	Sekine ^[59]	Porous prosthesis	Marlex	Animal
2003	Pfitzmann ^[58]	Homograft	Oesophagus	Human (1)
2004	Kim ^[57]	Porous prosthesis	Skin and polypropylene mesh	Animal
2005	Martinod ^[56]	Homograft	Allogenic aorta	Animal
2005	Shi ^[55]	Porous prosthesis	Polypropylene mesh with polyurethane/collagen	Animal
2006	Jaillard ^[54]	Homograft	Allograft aorta	Animal
2008	Sato ^[53]	Porous prosthesis	Polypropylene mesh with collagen	Animal
2008	Macchiarini ^[79]	Homograft	Stem cell seeded homograft	Human
2009	Nakamura ^[51]	Porous prosthesis	Polypropylene with additional collagen, stem cells	Animal
2010	Makris ^[50]	Homograft	Allograft aorta	Animal
2010	Sato ^[49]	Tissue engineering	Bioprosthesis	Animal
2010	Tsukada ^[74]	Tissue engineering	Bioprosthesis	Animal
2011	Yu ^[47]	Autogenous/prosthesis	Radial forearm flap with PTFE or polyethylene	Human (7)
2011	Jungebluth ^[48]	Tissue engineering	Stem cell bioartificial scaffold	Human (1)
2012	Elliott ^[46]	Tissue engineering	Stem cell bioartificial scaffold	Human (1)
2012	Gray ^[45]	Tissue engineering	Stem cell bioartificial scaffold	Animal
2012	Tani	Tissue engineering	Collagen scaffold with FGF	Animal
2012	Wurtz ^[77]	Homograft	Allograft aorta with fascial graft and external cartilage	Animal
2014	Chang ^[40]	Tissue engineering	Stem cell bioartificial (3D Printed) scaffold	Animal
2016	Delaere ^[78]	Allotransplant	Vascularised allograft	Human

¹A number of these are composite strategies. PTFE: Polytetrafluoroethylene; FGF: Fibroblast growth factor.

case today.

1990s ONWARDS

Further avenues of research have evolved in the last few decades. This has focussed on homografts, various composite strategies (including further work on porous prostheses) and latterly, tissue engineering^[1,5,9,10,12,14,40-67].

Scherer *et al*^[67] were first to experiment with bio-prostheses by transplanting tracheas from various animals as autografts, allografts and xenografts. Rejection seemed to be avoided^[31,67]. This preceded a plethora of animal studies, particularly transplantation studies, and in the last few years, attempts to translate this to patients^[40,41,43,44,49,50,54,56,61]. Recently, research has focused on tracheal stem cell regeneration. Despite initial positive results, the outcomes have been generally poor and as such should be used with caution^[42]. Pedicled flaps may serve to implant and maintain the stem cell generated trachea prior to reconstruction^[41]. A recent pilot study has used three-dimensional printing of an artificial tracheal graft^[40]. In addition, there has been some focus on the use of intestinal (either jejunal or oesophageal) tubes to replace the trachea^[66]. This autogenous tissue reconstruction can be categorised into free grafts with and without foreign material support (e.g., the composite wire and fascia or dermal grafts); vascularised tissue flaps (e.g., pedicled intercostal muscle) and autogenous tube construction (e.g., oesophagus)^[31]. Autologous tracheal replacement using radial forearm fasciocutaneous free flap has also demonstrated positive outcomes^[68].

Further homografts include pericardium and aorta^[50,54,56]. Patch repair of the trachea using pericardial allografts^[69] and xenografts^[70] have been shown to have good outcomes^[71]. More recently, aortic homografts used as a bioprosthetic device for patch repair have also shown favourable results^[72,73]. Circumferential replacement of the trachea using aortic allografts has shown poorer results, in both animal^[74] and human^[75] models. Wurtz demonstrated that silicone-stented aortic allografts have no cartilage regeneration, probably due to ischaemia prior to neoangiogenesis^[76]. This led to proposals of a composite, fascial flap-wrapped allogeneic aortic graft with external cartilage ring support^[77]. Again, no reconstruction has been as successful as direct anastomosis, or even silicone prostheses alone.

CONTROVERSIES AND FUTURE DEVELOPMENTS

The intriguing yet unsolved surgical dilemma of tracheal replacement remains a challenge to clinicians. Currently, work from the Leuven group (Delaere *et al*^[78]) have shown promising results with the judicious use of allotransplants. Surgical ingenuity will lead to novel approaches to these problems^[3]. However, it is important to note that these techniques should not create more problems than they

solve and patients are to be treated as an individual with a duty of care attached to that. As a corollary to this, it is worth highlighting that where a series of animal experiments are successful, application of these procedures to humans almost inevitably presents greater issues and a higher failure rate^[3]. Work on tracheal regeneration using stem-cell implanted scaffolds^[44,48,79], which has been the centre of recent controversy, showed questionable data and ultimately poor results.

CONCLUSION

Direct revascularisation of the trachea is unsuitable due to its lack of an intrinsic blood supply. Its anatomical features (proximity to major vessels, segmental blood supply) and the presence of a variety of different tissue types (respiratory epithelium, cartilage, blood vessels) make reconstruction difficult. Recent attempts with tissue-engineered transplants have all failed due to this reason^[80]. Tracheal reconstruction is optimal when primary anastomosis is possible with undue tension. Patients requiring reconstruction should be managed in a multidisciplinary team at a high volume tertiary referral centre to optimise treatment. Tracheal replacement can be divided into prosthesis, homograft and autogenous tissue reconstruction, or a combinatorial methodology. None have proven ideal conduits as tracheal replacements. The most convincing evidence has historically been silicone based prostheses, and more recently revascularised tracheal homografts and allotransplants. Stenting of the trachea has shown poor results. In emergent situations, endobronchial debulking and laser is preferable over stenting as this may prevent primary surgery.

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Retrospective Study

Esophageal squamous papilloma lacks clear clinicopathological associations

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Author contributions: Chan CHY designed the study and supervised manuscript preparation; Wu Y acquired study data; Weltman M supervised manuscript preparation; Jideh B acquired study data, reviewed the literature and wrote the paper.

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Abstract

AIM

To determine the prevalence of esophageal squamous papillomas (ESPs) in a tertiary teaching hospital and to assess for any clinical associations, including relations with esophageal squamous cell carcinomas (SCCs).

METHODS

Data from a total of 6962 upper gastrointestinal endoscopies over a five year period were retrospectively obtained and analysed.

RESULTS

ESP was found in sixteen patients (0.23%). Eight (50%) patients had a high body mass index, seven (44%) had history of cigarette smoking. Reflux esophagitis was found in four (25%) patients. All ESPs were solitary with a mean endoscopic size of 3.8 mm and located in the mid to lower esophagus. Human papilloma virus (HPV) was tested in three (19%) patients and was negative. Esophageal SCC was found in seven patients (0.10%) during the same period. None of the specimens were tested for HPV, and none had associated papillomatous changes.

CONCLUSION

ESP is an uncommon tumour with unclear clinical associations and malignant potential.

Key words: Esophagus; Papilloma; Gastroesophageal reflux disease; Human papilloma virus; Squamous cell

carcinoma

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Core tip: Esophageal squamous papilloma is a rare endoscopic finding with uncertain clinicopathological associations. They are usually asymptomatic and their aetiology is unknown. A high body mass index and a history of cigarette smoking, both risk factors for gastroesophageal reflux disease, were the most prevalent patient characteristic in our cohort with esophageal squamous papillomas (ESPs), however no definite associations can be established. None of the esophageal squamous cell carcinomas during the same study period progressed from ESP. Long-term longitudinal studies would be valuable to clarify clinical associations and the malignant potential of ESPs in order to establish appropriate management and surveillance strategies.

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INTRODUCTION

Esophageal squamous papilloma (ESP) is a rare tumour of the esophagus with a reported prevalence of 0.01% to 0.45%^[1-5]. Lesions rarely cause symptoms, and are usually an incidental finding on endoscopy. Typical endoscopic appearance is that of a small, less than 5mm sessile wart-like fleshy nodule (Figure 1) located predominantly in the middle to lower esophagus^[1,2]. Larger lesions with a more raised, erythematous appearance have also been described^[6]. The aetiology has not yet been established; proposed factors include chronic gastroesophageal reflux disease (GERD), human papilloma virus (HPV) and mucosal trauma^[5,7-13]. The clinical associations and malignant potential of these lesions is unknown. Currently, there is no consensus on appropriate management and surveillance strategies for ESPs. In this study we aimed to identify the prevalence of ESPs in an Australian tertiary hospital cohort and to assess for possible clinical associations. We also attempted to assess its association with esophageal squamous cell carcinoma (SCC).

MATERIALS AND METHODS

All patients between June 2010 and March 2015 with ESP and esophageal SCC at a tertiary teaching hospital (Nepean Hospital) were retrospectively identified using the electronic pathology department database. Over this period a total of 6962 upper gastrointestinal endoscopies were performed. Patients were identified and their

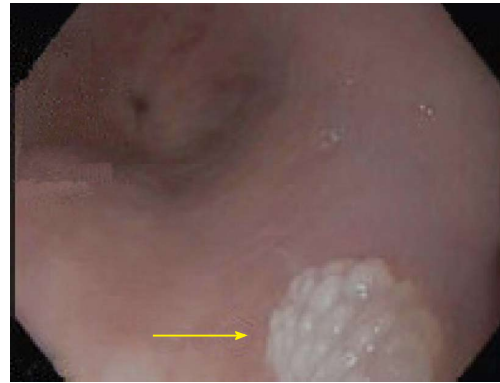


Figure 1 Esophageal squamous papilloma on upper endoscopy. A well demarcated soft wart-like sessile nodule with an estimated endoscopic size of 3 mm.

medical records and endoscopic reports were reviewed and analysed. The clinical information assessed included age, gender, body mass index (BMI), cigarette smoking history and use of acid suppression therapy [proton pump inhibitor (PPI)]. The endoscopic findings comprised the location, size and number of lesions; presence of a hiatus hernia, and presence of reflux esophagitis. Results of HPV testing were noted when performed; histology reports for patients with esophageal SCC during the same period were carefully perused for any papillomatous changes.

RESULTS

Among the 6962 upper gastrointestinal endoscopies performed over the study period, sixteen patients were found to have ESPs giving a prevalence of 0.23%. Patient characteristics are summarised in Table 1. The patients with ESPs comprised of ten (62.5%) females with mean age of 52 ± 16 (SD) years (range 33-83 years). Eight (50%) patients were overweight or obese having BMIs between 25-39; seven (44%) patients were cigarette smokers; three (19%) patients were using regular acid suppression therapy (PPIs). The indications for the endoscopic procedure varied with two of the sixteen patients having the procedure for investigation of GERD and one patient for dysphagia. One patient had evidence of a hiatus hernia, which was small. Reflux esophagitis was found in four (25%) of the sixteen patients. All patients had solitary papillomas; mean endoscopic size of lesions was 3.8 ± 3.2 (SD) mm (range 1-12 mm) and the mean size of histological specimens was 2.9 ± 1.5 (SD) mm (range 1-7 mm). All the papillomas were found in the middle to lower esophagus. Seven (44%) of them were biopsied; seven (44%) were removed with a polypectomy snare and details of the remaining two were not documented. Patients that had lesions biopsied did not have a repeat gastroscopy within the same study period for definitive resection of the lesion. Two (13%) patients had repeat endoscopies following endoscopic snare resection within the same study period and there was no evidence of papilloma recurrence. *Helicobacter*

Table 1 Patient characteristics with esophageal squamous papilloma

Patient No.	Age (yr)	Sex (M/F)	Cigarette smoking (Y/N)	BMI (Y/N)	PPI use (Y/N)	Indication for endoscopy	Location of ESP from incisors	No. of ESPs	Endoscopic size of ESP (mm)	Histological size of ESP specimen (mm)	Hiatus hernia (Y/N)	Reflux esophagitis (Y/N)	<i>Helicobacter pylori</i> (positive/negative)	HPV test (positive/negative)	Method of ESP resection/sampling
1	57	F	Y	20	N	Upper GI bleed	Distal	1	Small	2	N	N	Negative	n/a	n/a
2	83	F	N	19	Y	Dysphagia	20	1	3	3	N	Y	Negative	n/a	Snare polypectomy
3	66	M	N	24	N	Abdominal pain	32	1	Small	4	N	N	Negative	n/a	Snare polypectomy
4	74	M	N	36	N	Abdominal pain	39	1	Small	5	N	N	n/a	n/a	Hot biopsy
5	60	F	N	34	Y	GERD	33	1	4	3	Y (3 cm)	Y	Negative	n/a	Snare polypectomy
6	39	M	N	30	N	GERD	38	1	3	3	N	Y	Negative	Negative	Snare polypectomy
7	39	F	N	24	N	Bloating	28	1	3	2	N	N	Negative	n/a	Biopsy
8	33	F	N	21	N	Anaemia	27	1	Small	3	N	Y	Negative	n/a	Snare polypectomy
9	49	M	Y	30	N	Abdominal pain, family history CRC	Distal	1	Small	3	N	N	Negative	Negative	n/a
10	37	F	N	24	N	Family history of gastric cancer	32	1	1	1	N	N	Negative	Negative	Biopsy
11	54	F	Y	23	N	Variceal screen	35	1	2	4	N	N	n/a	n/a	Biopsy
12	39	M	Y	34	N	Abdominal pain	39	1	4	2	N	N	Negative	n/a	Biopsy
13	81	F	Y	28	N	Diarrhoea	25	1	Small	2	N	N	Negative	n/a	Biopsy
14	45	M	Y	31	Y	Abdominal pain	Upper third	1	2	2	N	N	Negative	n/a	Snare polypectomy
15	38	F	Y	n/a	N	Bloating, abdominal pain	25	1	n/a	1	n/a	n/a	Negative	n/a	Biopsy
16	41	F	N	27	N	Abdominal pain	35	1	12	7	N	N	Negative	Negative	Snare polypectomy

BMI: Body mass index; PPI: Proton pump inhibitor; CRC: Colorectal cancer; GERD: Gastroesophageal reflux disease; HPV: Human papilloma virus; n/a: Not available; ESP: Esophageal squamous papilloma; M: Male; F: Female; Y: Yes; N: No.

pylori was not evident on microscopy in any of the patients. HPV testing was performed on only three patient and all were negative.

Seven patients were observed to have esophageal SCC in the same period, giving a prevalence of 0.10%. Patient characteristics are summarised in Table 2. The group comprised of five (71%) females and with mean age of 71 ± 15 (SD) years (range 50-92 years). Two (29%) patients were overweight, one (14%) patient was underweight with a BMI of 18, and the remaining four (57%) patients had BMIs within healthy range. Three (43%) patients were cigarette smokers. HPV was not tested on any of the specimens. There were no reported papillomatous changes on histological examination.

DISCUSSION

In our study the prevalence of ESPs was 0.23% which is consistent with previously published studies^[1-5]. The majority of the patients were middle-aged also similar to previous studies in the literature. The female predominance in our cohort is an inconsistent observation compared to previous reports on ESPs^[1,7,8,14]. Although GERD has been postulated to be a factor in the aetiology of ESP^[5,9,15], only two (12.5%) of our study patients underwent upper endoscopy for GERD. However, we cannot ascertain with any certainty that the other patients did not have GERD. This is supported by the finding of reflux esophagitis in two (12.5%) patients who had the procedure for an indication other than GERD (one for the investigation of anaemia and the other for dysphagia, Table 1).

A high BMI was the most prevalent of the assessed patient characteristics in our study with 50% of patients having a BMI in the overweight-obese range. An association between BMI and ESPs has not been previously demonstrated. However, an elevated BMI is an established risk factor for GERD^[16]. The second most prevalent clinical characteristic in the studied patients was a history of cigarette smoking found in seven (44%) patients. Cigarette smoking was not found to be associated with ESP in a previous study^[14], but similar to a high BMI, cigarette smoking is a risk factor for the development of GERD^[17]. Hiatus hernia is another risk factor for GERD which was observed in one (6.25%) patient in our cohort and it was small-sized.

Table 2 Patient characteristics with esophageal squamous cell carcinoma

Patient No.	Age (yr)	Sex (M/F)	Cigarette smoking (Y/N)	BMI	Indication for endoscopy	Location of SCC from incisors (cm)	HPV test (positive/negative)	Papillomatous changes on histopathology	Management of SCC
1	50	M	Y	21	Dysphagia, B/G achalasia	40	n/a	No	Ivor-Lewis esophagectomy
2	92	F	N	29	Dysphagia	32	n/a	No	Palliation
3	62	F	Y	25	n/a	Middle	n/a	No	Ivor-Lewis esophagectomy
4	86	F	N	20	Dysphagia	15	n/a	No	Radiation therapy, Palliation
5	76	F	N	20	n/a	Middle	n/a	No	Neoadjuvant Chemo-Radiation, Ivor-Lewis esophagectomy
6	59	F	N	18	n/a	Middle	n/a	No	Ivor-Lewis esophagectomy, Chemotherapy, Palliation
7	72	M	Y	20	Dyspnoea, B/G achalasia	Distal	n/a	No	Radiation therapy, PEG tube feeding, Palliation

BMI: Body mass index; HPV: Human papilloma virus; SCC: Squamous cell carcinoma; n/a: Not available; M: Male; F: Female; Y: Yes; N: No.

The mean size and location of ESPs were consistent with previous observations^[1,2]. They were all solitary and appeared as rounded well delineated sessile wart-like lesions (Figure 1) as traditionally described. Multiple lesions have been observed in some studies^[18-20].

ESPs were not all removed with therapeutic intent, which is the general recommendation, despite the ambiguity about their malignant potential^[21]. Histological diagnosis remains important due to the endoscopic resemblance to other pathologies including glycogenic acanthosis, verrucoid border of SCC, and verrucous carcinoma^[2,21]. Case reports of alternative ablative techniques including radiofrequency ablation have been described^[22]. Recurrence after definitive endoscopic removal is thought to be low^[2]. This was true for the two patients in our series that had repeat gastroscopies within the same study period and no evidence of papilloma recurrent was found. It is unclear whether other lesions not endoscopically removed were not followed due to lack of well-established management and surveillance guidelines.

Three patients in our cohort had testing for HPV (serotype 16) in the ESP specimen and the results were all negative. Although HPV infection is a proposed aetiological factor since the demonstration of HPV antigens in ESPs^[23], the extent of the contribution is controversial and most reported lesions, similar to our study, are found in the absence of HPV^[2,13,14,24,25]. *Helicobacter pylori* has not been proposed to have any association in any of the previous ESP studies, and in our cohort the bacterium was not detected on microscopy in any of the patients.

The prevalence of esophageal SCC in this study was 0.10%. Most patients (71%) were females and generally older than the cohort with ESPs years. The risk of esophageal SCC, unlike esophageal adenocarcinomas, is not generally increased with obesity^[26] and this was true in our cohort with five (71%) patients having BMIs within healthy range. Cigarette smoking is an established risk factor for esophageal SCC and in our group three (43%) patients had a history of cigarette smoking.

HPV was not tested in any of the esophageal SCC specimens in our cohort, neither were any papillomatous changes reported. Whilst HPV infection and papilloma

formation are considered a precursor in cervical and oropharyngeal squamous carcinoma^[27,28], the relation between HPV and esophageal SCC is controversial with conflicting results across multiple studies. Several systematic reviews and meta-analyses have addressed this relation, two of the most recent by Li *et al.*^[29] and who Petrick *et al.*^[30] concluded that further studies are needed to clarify the association.

This study has several limitations. The study is a retrospective assessment of results which can lead to the possibility of inaccurate and incomplete data. It was performed in a single, tertiary-care institution which can introduce a selection bias. Most patients with ESP did not have follow-up gastroscopies to assess for ESP clearance or recurrence. Finally, the analysis of results is largely descriptive given the low prevalence and small absolute numbers of patients with ESPs making it difficult to draw conclusions on any clinical associations.

In summary, ESPs remains a rare endoscopic finding with uncertain clinicopathological associations. They are usually asymptomatic and their aetiology is unknown. Whilst a high BMI and a history of cigarette smoking, both risk factors for GERD, were the most prevalent patient characteristic in our cohort with ESP, no definite associations can be established. None of the esophageal SCCs during the same study period progressed from ESP. Long-term longitudinal studies would be valuable to clarify clinical associations and the malignant potential of ESPs in order to establish appropriate management and surveillance strategies.

COMMENTS

Background

Esophageal squamous papilloma (ESP) is a rare tumour with a reported prevalence of 0.01% to 0.45%. It is usually asymptomatic and discovered incidentally on upper endoscopy. The aetiology, clinical associations along with its malignant potential are unknown. The aim of this study was to determine the prevalence of ESPs in a tertiary teaching hospital and to assess for any clinical associations, including relations with esophageal squamous cell carcinomas (SCCs).

Research frontiers

There are limited studies on ESPs. Gastroesophageal reflux disease (GERD),

human papilloma virus (HPV) and mucosal trauma are proposed aetiological factors. No studies have assessed associations between ESPs and SCCs.

Innovations and breakthroughs

This study identified certain clinical features to be prevalent in patients with ESP including high body mass index and cigarette smoking, which have not been previously described. Also, the SCCs in the study period did not seem to progress from ESPs which may suggest ESP are benign.

Applications

This study contributes to the body of hypotheses surrounding ESP. Large longitudinal studies are required to help clarify clinicopathological associations of ESPs and their malignancy potential in order to establish appropriate management and surveillance strategies.

Peer-review

The authors aimed to identify the prevalence of ESPs in an Australian tertiary hospital cohort and to assess for possible clinical associations and to assess its association with esophageal SCC whose large data from a total of 6962 upper gastrointestinal endoscopies. Well written, well balanced.

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Retrospective Study

Efficacy of intragastric balloon on weight reduction: Saudi perspective

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Abstract**AIM**

To evaluate the safety and efficacy of intragastric balloon (IGB) in weight reduction in obese patients referred to a tertiary hospital in the Kingdom of Saudi Arabia.

METHODS

Three hundred and one consecutive obese individuals, who underwent IGB placement during January 2009 to May 2015, were analyzed. The subjects aged 18 to 60 years and had a minimum body mass index (BMI) of 27 kg/m². The IGB was placed under conscious sedation and kept for 6 mo. Anthropometric measurements were recorded during and after 6 mo of IGB removal.

RESULTS

The body weight, excess body weight, and BMI were significantly reduced at the time of IGB removal and 6 mo later. Body weight loss > 10% was achieved in 224 subjects at removal of IGB. End of treatment success and long-term success were both significantly observed in women (70 *vs* 11) (71 *vs* 12.5) respectively. Excess BMI loss was significantly higher in subjects retaining the IGB for over 6 mo both at the removal [43.44 ± 19.46 ($n = 221$) *vs* 55.60 ± 28.69 ($n = 80$); $t = 4.19$, $P = 0.0001$] as well as at the end of 6 mo' follow-up [46.57 ± 24.89 ($n = 221$) *vs* 63.52 ± 31.08 ($n = 80$); $t = 4.87$, $P = 0.0001$]. Within 3 d of IGB placement, two subjects developed pancreatitis and one subject developed cardiac arrhythmia. Intestinal obstruction due to displacement of IGB occurred in two subjects. All

these subjects recovered uneventfully after immediate removal of the IGB.

CONCLUSION

IGB was effective in our cohorts. The observed weight reduction was maintained for at least 6 mo post IGB removal. IGB placement was safe with a satisfactory tolerance rate.

Key words: Weight reduction; Intra-gastric balloon; Saudi

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Core tip: Intra-gastric balloon (IGB) is a minimally invasive option for weight reduction. Several studies have demonstrated its superiority to lifestyle changes in reducing the morbidity and mortality associated with morbid obesity. This study evaluated the safety and efficacy of Medsil IGB in weight reduction of patients referred for weight reduction to a tertiary center in the Kingdom of Saudi Arabia. Endoscopic placement and keeping the Medsil IGB in situ for six months was proven to be safe, well tolerated and very effective for short and long term weight loss.

Almeghaiseeb ES, Ashraf MF, Alamro RA, Almasoud AO, Alrobayan AA. Efficacy of intra-gastric balloon on weight reduction: Saudi perspective. *World J Clin Cases* 2017; 5(4): 140-147 Available from: URL: <http://www.wjnet.com/2307-8960/full/v5/i4/140.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v5.i4.140>

INTRODUCTION

Obesity, a medical condition in which body fat is accumulated in excess leading to severe negative health effects including reduced lifespan, affects an estimated 700 million people worldwide^[1]. This pandemic health problem is much more serious threat to public health even when compared to alcohol consumption or tobacco smoking. Obesity decreases life expectancy by 6 to 7 years^[2], while a body mass index (BMI) of 30-35 kg/m² and > 40 kg/m² reduces life expectancy by 2 to 4 years and by 10 years respectively^[3]. Some estimates have even predicted that a BMI of > 40 reduces life expectancy by almost 20 years^[4]. In addition to decline in the lifespan, this preventable cause of death also leads to quality of life deterioration owing to severe cardiologic, respiratory, dermatological, gastrointestinal, urinary, reproductive and psychiatric complications^[5]. A recent estimate published in 2013 has put the overall prevalence of obesity at 28.7% (body mass index \geq 30 kg/m²) in the Kingdom of Saudi Arabia, with women much more prone than men (33.5% vs 24.1%)^[6].

Advanced cases of obesity require surgical interventions with drastic lifestyle modifications. Alternatively, mild to moderately obese subjects can achieve 5%-10% weight loss through exercise and dietary changes^[7].

However, the weight gain recurs at high rates on cessation of these weight loss programs^[8]. Further, pharmacological agents have not been found to be any better than dietary and exercise programs. The therapeutic or lifestyle management of obesity is a long-term and arduous undertaking. Literature shows that long-term treatments, both dietary regimens and weight-loss programs following pharmacotherapy remain largely ineffective^[9]. Further, conservative treatment is clearly ineffective in morbid obesity (BMI \geq 40 kg/m²)^[10], while bariatric surgery remains the only option with promising long-term results. However, subjects who are unwilling to consent for or do not qualify for the bariatric surgery end up having intra-gastric balloon as the best possible alternative^[11].

These factors have fostered a spurt in interest in the utility of intra-gastric balloon (IGB) to achieve weight loss in excess of 10%. While earlier studies have documented the utility of various intra-gastric balloons in Saudi subjects^[12,13], data on newer variants of balloons is lacking. Hence, this study is an attempt to evaluate the end of treatment success rates (ETS) and long-term treatment success rates (LTS) for recently introduced, GOST R certified intra-gastric balloon MEDSIL[®] in obese patients referred to a tertiary health clinic in the Kingdom of Saudi Arabia.

MATERIALS AND METHODS

Subjects

Three hundred and one subjects, consecutively opting for IGB therapy for weight loss at The Prince Sultan Military Medical City Hospital, Kingdom of Saudi Arabia between January 2009 and May 2015 were included in the study. Both men and women aged 14 to 65 years with a minimum BMI of 27 kg/m² and medically free from or with one or two of the comorbidities namely diabetes mellitus, hypertension, bronchial asthma, back pain, or Knee joint complains were included. In general, patients rated only up to ASA class II were preferred. Further, subjects without active endocrine diseases and ability to tolerate the procedure were selected for the procedure. Patients classified into \geq ASA category were excluded from the procedure. Baseline characteristics of the study subjects are presented in Table 1.

All the subjects underwent a routine clinical examination where information on anthropometrics and medical history was collected. Weight and height was measured with patients wearing no shoes and light clothing. Fasting blood sample was collected in the morning for the estimation of blood glucose concentration. Subsequent to the clinical evaluation of these results and after obtaining an informed written consent, MEDSIL[®] IGB was placed in the stomach through endoscopy.

Intra-gastric balloon implantation and removal

All the subjects were treated with MEDSIL[®] IGB, silicon based saline filled bioenergetic intra-gastric balloon (BIB) with a maximal volume of 700 mL (CSC MEDSIL, Russia). Patients were explained all the risks including perforation,

Table 1 Baseline characteristics of the subjects (*n* = 301) included for intra-gastric balloon therapy

Characteristics	Average (mean \pm SD) ¹	Range
Age (yr)	34.34 \pm 10.38	14-65
Female (%)	67	
Body weight (kg)	94.73 \pm 16.38	67-203
Height (cm)	161.52 \pm 6.11	150-179
BMI (kg/m ²)	36.24 \pm 5.24	27.10-70.24
Excess body weight (ideal BMI 25)	29.42 \pm 14.61	5.6-130.8
Fasting blood glucose (mg/dL)	100.15 \pm 29.26	69-240

¹Applicable to all the values except % females. BMI: Body mass index.

bleeding, infection and adverse effects to the medicine, as well as the benefits and alternatives to the procedure prior to obtaining the informed written consent. All the patients understood the details and stated so.

For insertion of balloon, the patient was connected to monitoring devices and placed in left lateral position. In 297 patients, the device was implanted under procedural sedation and analgesia, with midazolam and fentanyl or pethidine. In 4 patients, the device implantation was done by inducing anesthesia using midazolam and intravenous propofol. Oxygen was provided continuously through a nasal cannula. Intravenous medications were administered through an indwelling cannula. After adequate conscious sedation was achieved, the patient was intubated and the endoscope was advanced under direct visualization to the duodenum.

Endoscope was withdrawn after complete examination for the presence of grossly anatomical contraindications. Balloon was inserted into the oral cavity and pushed into the stomach with a trocar followed by re-introduction of the endoscope. Under direct visualization, balloon was adjusted for proper placement followed by retraction of the push trocar wire. Balloon was then inflated with 400 mL to 700 mL of saline mixed with methylene blue. On achieving the desired inflation, the balloon catheter was gently pulled out leaving the balloon in stomach. The scope was gently retracted with careful examination of the colour, texture, anatomy, and integrity of the mucosa on the way out. The patient was subsequently transferred to the recovery area for observation.

The IGB was removed on completion of 6 mo, with the duration extending by one or more months in some subjects owing to various reasons. Anthropometric measurements were recorded during and after 6 mo of IGB removal. Overnight fasting blood specimen was collected at removal for the estimation of blood concentration. Patients were also provided with walk in follow-ups/clinic appointments on quarterly basis, but two third of the patients were seen on the fixed appointment only.

Similar protocol was followed for the removal of the balloon. After achieving adequate conscious sedation, the patient was intubated and the scope was advanced under direct visualization to the Stomach. After confirming absence of food or organic particles, an aspiration needle

was inserted into the balloon followed by complete withdrawal of the fluid. The fully deflated balloon was withdrawn using a toothed forceps along the scope followed by routine follow up procedures.

Patients remained on their regular food without prescription of a hypocaloric diet. Post-insertion fasting blood glucose level estimation were scheduled and followed up to ensure that it was done as soon as treatment duration is completed.

Measurements and statistics

Weight loss variables like body weight (kg), BMI, body weight loss (BWL%) and excess BMI loss (EBL%) were measured at baseline, and during and after 6 mo of IGB removal. A BWL value of > 10% at the time of IGB removal and after 6 mo of IGB removal was considered an ETS and LTS respectively. EBL% was calculated using the formula [(Baseline BMI-Current BMI)/(Baseline BMI-25)] \times 100. All the descriptive data are expressed as mean \pm SD. Paired *t*-test was used to compare baseline and outcome variables for individuals, whereas unpaired *t*-test was used for gender and age based comparisons. Fisher's exact test was used to evaluate the occurrence of number of patients with BWL% > 10 between groups. The association of initial BMI and age with BWL% and EBL% was measured through Pearson correlation coefficient. A two-tailed *P* value of < 0.05 was considered statistically significant. Statistical Package for the Social Sciences (SPSS v. 18) was used for all the statistical tests.

RESULTS

Apart from the expected post procedure symptoms like nausea, vomiting and upper abdominal discomfort, and no serious complications were observed during recovery from IGB placement. Balloon was removed a day to week earlier than 6 mo in 20 subjects, at the completion of 6 mo in 201 subjects and after a week to few months over 6 mo in 80 subjects. In addition to the removal of IGB in 221 subjects owing to completion of the treatment duration, balloons were removed due to numerous other reasons as listed in the Table 2.

At the end of treatment, body weight, excess body weight, and BMI were significantly lowered as compared to initial measurements (Table 3 and Figure 1). The ETS rate, represented by number of patients with BWL% of > 10 was 74% (224 of 302 subjects). The fasting blood glucose remained statistically similar to the initial measurements. At the end of 6 mo after IGB removal, the body weight, excess body weight and BMI still remained significantly lower (Table 3). The BWL and BMI loss continued during post IGB removal phase, resulting in significantly higher measurements after 6 mo of removal as compared to the measurements taken during IGB removal. The LTS rates remained similar to ETS with just 2 more subjects added to the > 10% weight loss by the end of 6 mo IGB post-removal.

Statistical sub-analysis revealed different outcome

Table 2 Reasons for removal of the intra gastric balloon

Reason for removal	No.	Reason for removal	No.
TDC	221	Intolerance	4
Abdominal pain	1	Vomition	1
Miscellaneous	2	TDC and intolerance	1
TDC and abdominal pain	19	TDC and vomition	10
TDC and discomfort	24	TDC and other reasons	2
Intolerance and abdominal pain	4	Intolerance and vomition	2
Intolerance and other reason	1	Abdominal pain and vomition	3
Abdominal pain and other reason	1	Discomfort and other reason	1
TDC, abdominal pain and vomition	1	Intolerance, abdominal pain and vomition	2
TDC, abdominal pain and discomfort	1		

Abdominal discomfort was a state of tolerable uneasiness without pain; Abdominal pain involved a state of colic; Vomition was a state of uncontrolled expulsion of gastric contents; Intolerance was a state wherein subjects experienced a mix of side effects and were unable to tolerate. Other reasons were a variety of situations that did not show a consistent pattern. TDC: Treatment duration complete.

Table 3 Weight related measurements at intra gastric balloon removal and after 6 mo of removal

Characteristics	At removal (mean \pm SD) ^a	After 6 mo of removal
Body weight (kg) (Min-Max)	82.25 \pm 14.73 ^b (55-181)	81.06 \pm 14.84 ^b (53-181)
BWL (kg) (Min-Max)	12.48 \pm 5.16 (0-30)	13.67 \pm 6.65 ^b (-1-42)
BWL (%) (Min-Max)	13.08 \pm 4.81 (0-35.29)	14.30 \pm 6.12 ^b (-0.85-32.14)
No. of patients with BWL% > 10	224	226
Excess body weight (ideal BMI 25) (Min-Max)	16.93 \pm 13.44 ^b (-10.61-108.75)	15.74 \pm 13.73 ^b (-12.72-107.04)
BMI (kg/m ²) (Min-Max)	31.49 \pm 4.88 ^b (20.96-62.63)	31.04 \pm 5.01 ^b (20.44-63.14)
BMI loss (kg/m ²) (Min-Max)	4.75 \pm 1.87 (0-11.43)	5.20 \pm 2.40 ^b (-0.36-15.43)
EBMIL% (Min-Max)	46.67 \pm 22.88 (0-161.09)	51.07 \pm 27.66 ^b (-2.12-195.53)
Fasting blood glucose (mg/dL) (Min-Max)	98.67 \pm 20.28 (71-187)	--

^a*P* < 0.05 vs ^b*P* < 0.001. BWL: Body weight loss; BMI: Body mass index; EBMIL: Excess BMI loss.

Table 4 Association of gender and exercise on end of treatment success and long term success

Characteristics	At removal (mean \pm SD) ^a				After 6 mo of removal	
	Gender		Exercise		Gender	
	Male (<i>n</i> = 72)	Female (<i>n</i> = 229)	Yes (<i>n</i> = 131)	No (<i>n</i> = 170)	Male (<i>n</i> = 72)	Female (<i>n</i> = 229)
BWL (%)	14.99 \pm 4.72	12.48 \pm 4.68 ^b	15.22 \pm 4.81	11.43 \pm 4.11 ^b	16.71 \pm 6.72	13.53 \pm 5.72 ^b
Number of patients with BWL% > 10	8	160 ^b	113	111 ^b	9	163 ^b
Body mass index loss (kg/m ²)	5.56 \pm 1.92	4.49 \pm 1.78 ^b	5.47 \pm 1.85	4.19 \pm 1.68 ^b	6.19 \pm 2.72	4.89 \pm 2.20 ^b
EBMIL%	51.61 \pm 24.75	45.12 \pm 22.09 ^a	55.66 \pm 25.12	39.74 \pm 18.24 ^b	57.48 \pm 30.27	49.06 \pm 26.53 ^a
Fasting blood glucose reduction (%)	-0.59 \pm 13.29	-0.92 \pm 13.14	-0.37 \pm 13.10	-1.25 \pm 13.22	--	--

^a*P* < 0.05 vs ^b*P* < 0.001. ETS: End of treatment success; LTS: Long term success; BWL: Body weight loss; EBMIL: Excess body mass index loss.

when patients were compared according to gender and exercise habits (Table 4). The BWL%, BMI loss, and excess BMI loss (EBMIL%) was significantly lesser in women at the end of treatment as well as after 6 mo of removal. However, significantly higher proportion of women achieved ETS (70 vs 11) and LTS (71 vs 12.5) rates. As expected, BWL%, BMI loss and EBMIL% was significantly higher in exercising cohort at the end of treatment. Fasting blood glucose level changes remained statistically similar with gender and exercise habit.

Age was not correlated with initial BMI or EBMIL% at initial or later phases of the study (Table 5). However, initial BMI was strongly correlated with BMI as well as EBMIL% measured at IGB removal as well as 6 mo after removal.

The duration of IGB removal was also important in

determining the EBMIL% (Figure 2). The EBMIL% was significantly higher in subjects retaining the IGB for over 6 mo both at the removal [43.44 \pm 19.46 (*n* = 221) vs 55.60 \pm 28.69 (*n* = 80); *t* = 4.19, *P* = 0.0001] as well as at the end of 6 mo follow-up [46.57 \pm 24.89 (*n* = 221) vs 63.52 \pm 31.08 (*n* = 80); *t* = 4.87, *P* = 0.0001]. Duration of the IGB was also important in determining adverse complications in some of the individuals as outlined below.

In addition to the routine adverse events associated with IGB therapy, some of the patients experience unusual complication of spontaneous deflation and passage out of the digestive system. It must be noted that most of these patients had the balloon beyond the treatment duration. Out of five such cases, 2 women who had undergone IGB insertion at other institute, consulted us for removal after

Table 5 Correlation of age and initial body mass index with weight-linked parameters

	Age	Initial BMI	BMI at removal	EBMIL% at removal	BMI after 6 mo of removal	EBMIL% after 6 mo of removal
Age	1	0.074	0.082	-0.108	0.082	-0.108
Initial BMI	0.074	1	0.934 ^b	-0.413 ^b	0.891 ^b	-0.376 ^b

Values are Pearson Correlation Coefficient (r); ^bP < 0.01. BMI: Body mass index; EBMIL: Excess BMI loss.

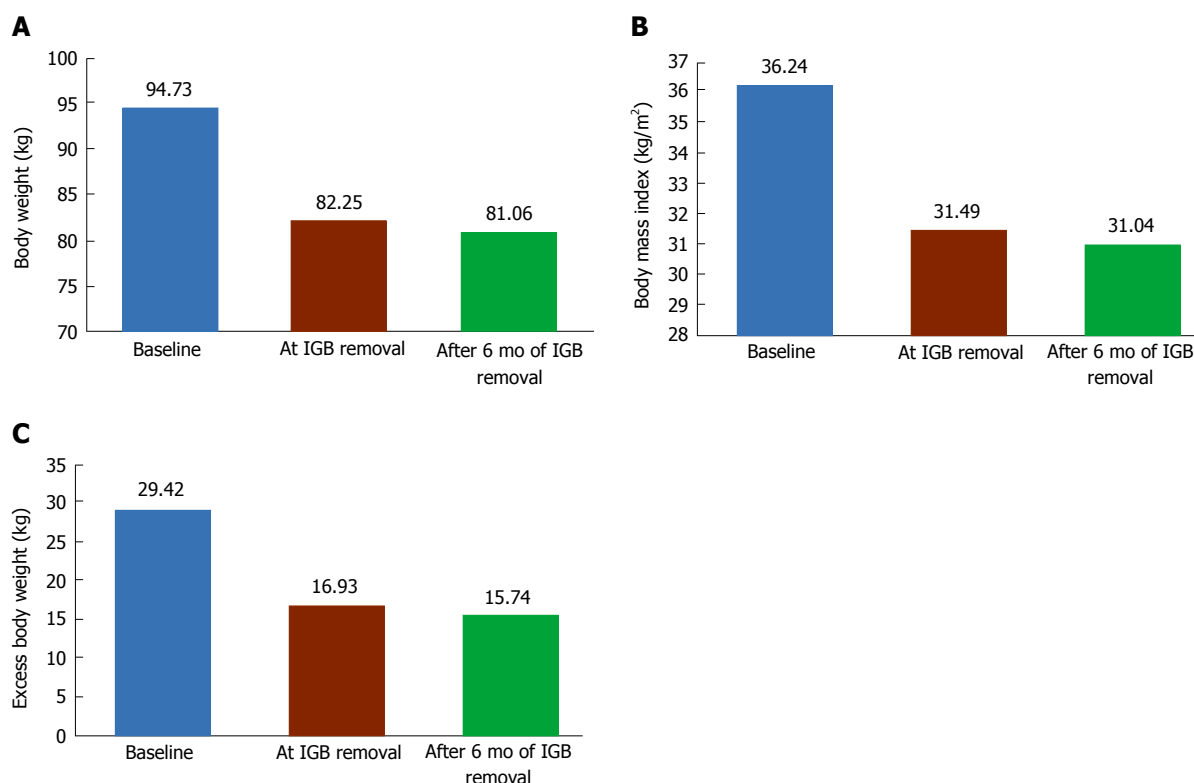


Figure 1 From baseline to 6 mo follow-up. A: Body weight changes. Both the measurements were significantly lower than baseline values; B: Body mass index changes. Both the measurements were lower than baseline values; C: Excess body weight changes. Both the measurements were significantly than baseline values. IGB: Intra gastric balloon.

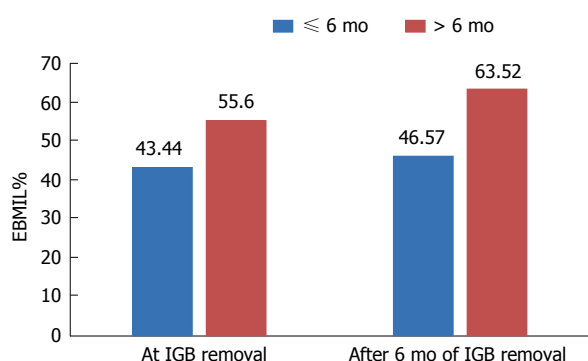


Figure 2 Influence of duration at intra gastric balloon removal excess body mass index loss%. The red bars are statistically larger than bars. IGB: Intra gastric balloon.

1 year of insertion and three women operated at our clinic approached for removal at 8 mo. These five women underwent gastroscopy using X-ray and CT scan, which failed to reveal any traces of the IGB in the GI tract. The

only plausible explanation for this is spontaneous rupture and excretion of the IGB without any knowledge of these patients.

One woman and one man developed clinical and biochemical pancreatitis on third day post IGB insertion. These symptoms subsided completely after immediate removal of IGB. One man developed arrhythmia 2 d post IGB insertion and recovered fully following immediate removal of IGB.

A woman with IGB got pregnant before the due date of removal and approached us at the end of first trimester with symptoms correlating intestinal obstruction. Esophagogastroduodenoscopy failed to detect balloon in the stomach. Imaging showed that balloon was lodged in middle of the jejunum. This IGB was surgically removed. The woman completed pregnancy without complications and gave birth to a normal offspring. Another man developed intestinal obstruction due to IGB dislodgement 7 mo post insertion that was detected through abdominal CT scan. This man recovered completely and uneventfully

Table 6 Studies reporting outcomes in body composition after placement of intra-gastric balloon

Study	Weight loss at removal (duration of placement in months)	Weight loss at follow-up (duration of follow-up in months)
Mathus-Vliegen <i>et al</i> ^[26] , 2005	21.3 (12)	12.6 (12)
Herve <i>et al</i> ^[27] , 2005	12.0 (6)	8.6 (12)
Doldi <i>et al</i> ^[28] , 2004	15.5 (6)	-1.3 (14)
Melissas <i>et al</i> ^[29] , 2006	41.6% EWL (6)	23.9% EWL (6-30)
Angrisani <i>et al</i> ^[30] , 2006	32.9% EWL (6)	27.1% EWL
Ganesh <i>et al</i> ^[31] , 2007	4.4 (6)	1.5 (6-12)
Ohta <i>et al</i> ^[32] , 2009	12 (6)	6.4 (12)
Gümürdülü <i>et al</i> ^[33] , 2013	12.4 (6)	9.7 (6)
Bužga <i>et al</i> ^[20] , 2014	18.4 (6)	-
Present study	13.08 (6)	14.30 (6)

Weight in kilograms; EWL: Excess weight loss.

after laparoscopic surgery.

DISCUSSION

Subsequent to their introduction in 1982^[14], numerous studies showed that IGBs are an effective and low cost method to achieve temporary weight loss in morbidly obese individuals, leading to significant decrease in morbidity and mortality rates^[15,16]. The promising outcomes have fuelled the development of numerous fluid or air filled IGBs over the years. The newer variants are becoming much less invasive compared to surgical interventions in morbid obesity, though latter options remain primary approach in super-obese patients with a BMI over 50^[17]. IGBs are also employed as a preoperative tool in bariatric surgery as its weight reducing effects significantly reduces the mortality, morbidity and risks associated with this invasive surgery^[18].

Variety of intra-gastric balloons have been studied in numerous studies for safety and efficacy in Saudi subjects^[12,19]. However, the newer variant of intra-gastric balloon Medsil remains to be tested in this population. In this study, we tested the end of the treatment and long term success rates for this device in a large Saudi cohort. Similar to a 2014 report on Czech subjects^[20], these balloons were well tolerated in Saudi subjects analysed in this study.

This study demonstrated a clear benefit of Medsil balloon on body composition, as six mo placement of the balloon lead to significant reduction in body weight. The mean BMI loss (4.75 and 5.20 kg/m²) and BWL (13.08 and 14.30 kg) at IGB removal and after six months of removal were comparable to both the results of using other balloons or Medsil balloons. These studies have reported a BMI loss of 5.7-6.7 kg/m² and weight loss of 14.7-17.8 kg^[16,21,22], with one study using the same device reporting a BMI loss of 5.5 kg/m² and weight loss of 18.4 kg^[20]. Table 6 presents a comparison showing the similarities of outcomes in body composition reported by earlier studies. It must be noted that the BMI loss which corresponds to weight-loss was on the higher end as

compared to other studies after one year of completion of the treatment.

Two reviews have extensively evaluated the weight loss due to IGBs. Dumonceau^[21] 2008 analysed 4877 patients from 30 studies and recorded a mean weight loss of 17.8 kg (or a BMI loss of 4-9 kg/m²). Another systematic review reported similar outcomes and revealed that, combined with lifestyle changes, IGBs provide an effective means for achieving a significant temporary weight loss, though the long term outcomes remain yet to be understood^[16]. Our results of a significant weight loss and a large number of patients achieving and maintaining > 10% BWL from the IGB removal to follow-up after 6 mo, clearly suggests that long term results can be achieved through this method. In addition to the balloon, initial BMI, adherence to the lifestyle changes and patients level of motivation are highly likely to play an important role in achieving long term results.

Bioenteric intra-gastric balloons, which are now known as Orbera Intra-gastric Balloon (Apollo Endosurgery, Austin, TX, United States) are the most commonly used balloons. A comparison with the existing literature showed that BWL was less than expected, however not too less (Table 7).

The number of individuals achieving > 10% BWL increased from 224 to 226 from balloon removal to at 6 mo follow-up. This amounts to an increase in the number of patients achieving > 10% BWL during follow-up. These results are highly impressive as two of the earlier studies have showed that only 48%^[23] or 55%^[24] of the patients went on to continue losing weight from balloon removal to follow-up at 1 year. Our study results are very promising in this aspect.

The fasting blood glucose level remained statistically similar both during balloon removal as well as after 6 mo of follow-up. Bužga *et al*^[20] 2014 also reported a similar result, though they demonstrated a positive effect of the balloon on glucose tolerance. On the contrary, earlier studies by Mathus-Vliegen and Konopko-Zubrycka have demonstrated a statistically significant reduction in fasting blood glucose levels through intra-gastric balloons^[11,24]. These contradictory findings remain to be evaluated by meta-analysis to reveal the actual association.

Our study, though of higher strength due to large sample size, had a few limitations. A follow-up period of more than six months (at least 1 year) including tracking of comorbidities along with body conversion parameters would have been more insightful. The evaluation of fasting blood glucose levels could have been more meaningful if glucose tolerance and glycated hemoglobin levels were also included. Compared to earlier report of maintenance of > 10% weight loss in about 25% of patients for almost 30 mo^[25], 75% of the subjects who achieved this result after 6 mo follow-up in our study seem to be responding much better. Looking at the similarities of BIB and Medsil balloons, it is highly likely that our subjects will be able to maintain weight loss for long term. However, it must be noted that our study provides the first report on the follow-up parameters for

Table 7 Comparison of weight-loss with other types of intra-gastric balloons

Balloon	Type (volume)	Material	Weight loss (EOT in months)	Ref.
Medsil BIB	Fluid-supplied (400-700 mL saline)	Silicone	12.48 ± 5.16 kg (6 mo)	This study
Orbera (Apollo Endosurgery)	Fluid-supplied (400-700 mL saline)	Silicone	16.9 ± 0.9 kg (6 mo)	Gaur <i>et al</i> ^[34] , 2015
The Elipse™ (Allurion Technologies)	Fluid-supplied (450-550 mL filling fluid)	NA	2.4 kg (6 wk)	Machytka <i>et al</i> ^[35] , 2016
ReShape Duo® Integrated DualBalloon System (ReShape medical)	Fluid-supplied (900 mL; 450 mLX2 saline)	Silicone	25.1 ± 1.6% EWL (6 mo)	Ponce <i>et al</i> ^[36] , 2015
Spatz Adjustable Balloon system (Spatz FGIA)	Fluid-supplied (400-600 mL saline)	Silicone	24 kg (at 12 mo)	Brooks <i>et al</i> ^[37] , 2014
Heliosphere BAG® (Helioscopie)	Air-supplied (950 mL air)	Polyurethane and silicone	16 ± 7 kg (6 mo)	Giardiello <i>et al</i> ^[38] , 2012
Obalon® Gastric Balloon (Obalon Therapeutics)	Air-supplied (250 mL air, nitrogen)	NA	5 kg (12 wk)	Mion <i>et al</i> ^[39] , 2013

EOT: End of treatment; EWL: Excess weight loss; NA: Not available; BIB: Bioenteric intra-gastric balloon.

Medsil balloons.

In conclusion, it could be concluded that Medsil intra-gastric balloons are safe and effective for Saudi subjects and more than three fourth of the subjects can be expected to achieve long term weight loss.

COMMENTS

Background

Obesity is a major pan-endemic health problem in the Kingdom of Saudi Arabia affecting about 30% of the population. Literature shows that dietary regimens and weight-loss programs following pharmacotherapy remain largely ineffective. Bariatric surgery is the most effective long term option, however the majority are either reluctant to undergo surgery or do not qualify for medical reasons.

Research frontiers

Intra-gastric balloons are of proven benefit as an alternative or a bridge to surgery, however the evidence for its utility particularly the newer version such as the intra-gastric balloon (IGB) MEDSIL® in the Kingdom of Saudi Arabia is lacking.

Innovations and breakthroughs

This study is an attempt to evaluate its long-term treatment success rate in obese patients referred to a tertiary health clinic in the Kingdom of Saudi Arabia. Endoscopic placement and keeping the Medsil IGB in situ for six months was proven to be safe, well tolerated and very effective for short and long term weight loss.

Applications

The intra-gastric balloons are well tolerated and are effective in weight reduction.

Peer-review

It is a retrospective study but of a very big cohort and the IGB is a new commercialized one. It is a well done paper and the language is good too.

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Incidental echocardiographic finding: Fractured inferior vena cava filter

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Abstract

Inferior vena cava filters have gained increasing popularity in recent decades and knowledge on rare complications becomes vital to practicing physicians. A 30-year-old African American male with diabetes mellitus, hypertension, end-stage renal disease, history of deep venous thrombosis and placement of venacaval filter who was seen in the cardiology clinic for cardiac risks stratification prior to renal transplant. Patient denied any cardiac symptoms. A transthoracic echocardiogram was performed and showed two linear echoes bright densities in the right atrium and right ventricle embedded which was later found to be fractured filter struts by computed tomography. We discuss the various outcomes associated with non-retrieval of retrievable inferior vena cava filters.

Key words: Inferior vena cava filter; Fractured inferior vena cava filter; Cardiac foreign body; Metal in heart; Incidental echocardiographic finding

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Core tip: Retrievable vena cava filters as indicated by the name, is temporary and should be retrieved timely. However noncompliance to follow-up and retrieval has been associated with numerous complications which could also be life threatening in extreme cases. We are writing this case with the intent to enlighten physicians on various types of available filters, complications associated with it and the challenges associated with delayed retrieval of filters. This case report also emphasizes the challenges associated with delayed retrieval of the filters and the management of the complications associated with inferior vena cava filters.

Sivasambu B, Kabirdas D, Movahed A. Incidental echocardiographic finding: Fractured inferior vena cava filter. *World J Clin Cases* 2017; 5(4): 148-152 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v5/i4/148.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v5.i4.148>

INTRODUCTION

Intracardiac foreign bodies have been described in the literature with the first case described in 1954. Various post traumatic and iatrogenic cardiac foreign bodies have been implicated with catheters fragments, needles, pacemaker electrodes, and stents being the commonest. We describe an asymptomatic patient who was found to have an intra cardiac foreign body on a transthoracic echocardiogram done for preoperative evaluation for renal transplant. On further evaluation it was confirmed as inferior vena cava (IVC) filter fragments.

Vena cava filters have gained increasing popularity in recent decades with the simplicity of the procedure, and the expansion of the indications including prophylactic insertion especially in patients following trauma with high risk for venous thromboembolism. Thus knowledge about the possible complications associated with IVC filters becomes vital for practicing physicians. Fracture of IVC filters and intra cardiac embolization can lead to potentially life threatening complications.

CASE REPORT

A 30-year-old African American male with diabetes mellitus, hypertension and end-stage renal disease was seen in the cardiology clinic for cardiac risk stratification prior to renal transplant. Patient denied any cardiac symptoms and stated to have good functional status. One year prior he had sustained a motor vehicle accident with extensive burn injuries and fracture of the left tibia and fibula for which he had an external fixation performed. His hospital course was complicated by deep venous thrombosis (DVT) for which he underwent placement of an IVC filter. On examination pulse rate was 78, arterial pressure was 140/88 mmHg and respiratory rate was 14. Physical examination was remarkable for scars in chest and extremities from prior burns treated with skin graft. Cardiovascular examination revealed normal heart sounds with no gallops or murmurs and no volume overload. Electrocardiogram showed normal sinus rhythm. The transthoracic echocardiogram showed two linear echo bright densities in the right atrium (Figure 1) and ventricle embedded in the wall (Figures 2 and 3) otherwise unremarkable. Non-contrast computed tomography of the chest confirmed the presence of the foreign bodies which was identified to be the fractured limbs of the IVC filter (Figures 4 and 5). IVC filter was in place with the missing limbs evident on imaging (Figure 6). As patient was asymptomatic and the objects were found to be embedded in the myocardium vena cava

filter retrieval was not advocated. Though the indication for IVC filter placement was transient patient had lost to follow-up and now presented with an incidental intra cardiac foreign body.

DISCUSSION

The Mobin-Uddin umbrella filter^[1] was the initial filter of historical value followed by the Greenfield filter which was introduced in 1973 by Greenfield *et al*^[2] and still remains the standard to which other filters are compared. Vena cava filter is utilized as a treatment option of venous thromboembolism in specific situations. Venous thromboembolism (VTE) comprises of deep venous thrombosis and pulmonary embolism (PE). VTE is known to be associated with increased morbidity and mortality. The gold standard treatment for DVT and PE is anticoagulation. However in the presence of contraindication for anticoagulation or if significant risk of bleeding persists vena cava filters are the safest treatment modality^[3,4]. Vena cava filters can also be placed for treatment failure of anticoagulation and recurrent thrombosis despite therapeutic levels of anticoagulation and development of new contraindications after initiation of anticoagulation. In the latter however the decision of placement depends on the required duration of anticoagulation and the risk of thrombosis on cessation of anticoagulation.

Vena cava filters (IVC filters) are commonly placed in the IVC below the level of renal veins owing to the high prevalence of lower extremity thrombosis and subsequent pulmonary embolism. Even in the absence of demonstrable Lower extremity thrombosis in pulmonary embolism, IVC filters are placed if anticoagulation is contraindicated as thrombus in the pelvis or calf veins may be undetected or can form later. Nevertheless in the context of upper extremity thrombosis IVC filters are not beneficial and superior vena cava filters should be placed.

Utilization of IVC filters for DVT varies widely and has been recently evaluated in a study in 263 hospitals. Approximately 15% of the patients with venous thromboembolism received filter placement with a wide range between 0% to 39%. The characteristics associated with the wide variability in filter placement were acute bleeding at the time of admission, major operation after admission, presence of metastatic cancer, more severe illness, small hospital, and rural location.

Various types of IVC filters are available for use currently and can be classified as permanent and retrievable filters. The Society of Interventional Radiology guidelines recommends that the decision to select between the permanent and retrievable filter should be based on required duration of treatment for venous thromboembolism and the risks associated with anticoagulation therapy^[5]. Complications are associated with both type of filters but the prevalence of complications varies with each specific type of IVC filter. Complications could be directly associated with the insertion of the filter such as bleeding or infection at the puncture site, allergic reactions to contrast or

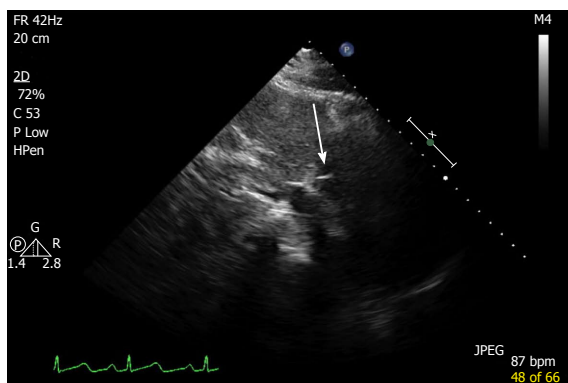


Figure 1 Echocardiography - modified subcostal view showing liner foreign body in the right atrium.

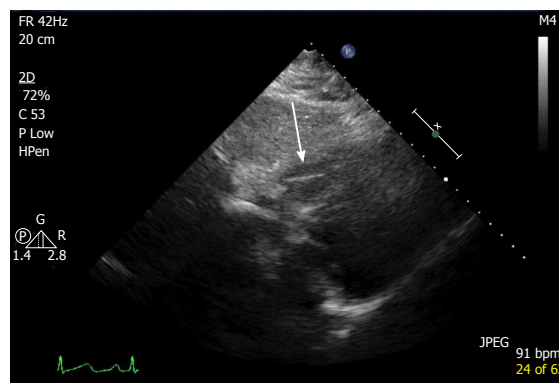


Figure 2 Echocardiography subcostal view showing liner foreign body in the right ventricle.

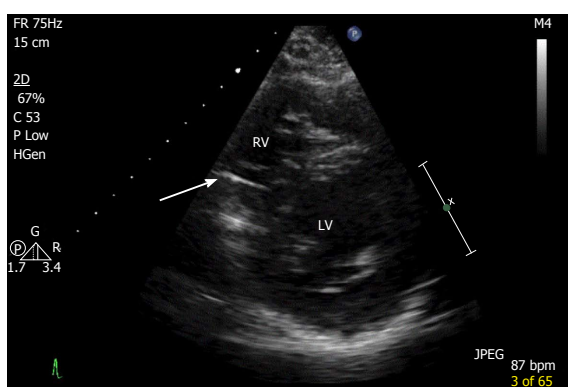


Figure 3 Echocardiography short axis view showing liner foreign body in the right ventricle.

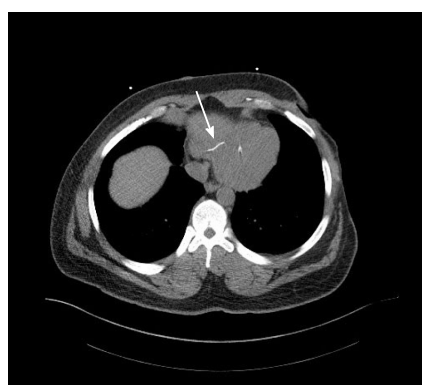


Figure 4 Computed tomography of the chest showing liner foreign body in the right ventricle.



Figure 5 Computed tomography of the chest showing liner foreign body in the right ventricle.

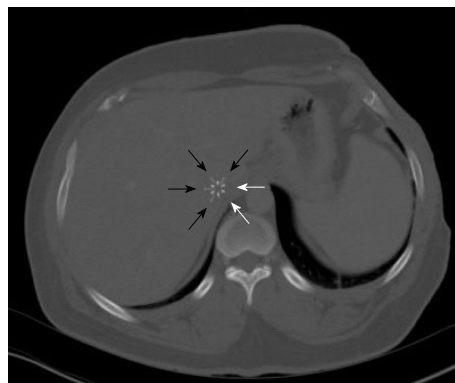


Figure 6 Computed tomography of the abdomen showing missing limbs of the filter. Black arrows showing 4 outer limbs and white arrows showing the position of missing outer limbs.

other medications used during placement, misplacement of the filter and entrapment of the guidewire within the filter. Late complications include fracture, migration, limb embolization, tilt, IVC penetration, VTE and IVC thrombus^[6,7].

A review of data from the United States Food and Drug Administration Manufacturer and User Facility Device Experience (MAUDE) from January 2009-December 2012 revealed 1606 reported AEs involving 1057 IVC filters were identified. Of reported AEs, 1394 (86.8%)

involved retrievable IVC filters, and 212 (13.2%) involved permanent IVC filters ($P < 0.0001$). Reported AEs included fracture, migration, limb embolization, tilt, IVC penetration, venous thromboembolism and pulmonary embolism, IVC thrombus, and malfunctions during placement.

IVC filters mechanically provide protection from lower extremity DVT migration to the lungs however does not protect against thrombosis at or below the filter. Knowledge on management of IVC filter thrombosis

is limited to experience with small group of patients. Various techniques have been utilized with endovascular treatment being more successful. Other techniques such as catheter-directed thrombolysis, power pulse spray, various mechanical devices, judicious use of tPA or stent placement have also been used in case by case basis.

Though the most reported complication with retrievable filter was fracture according to the MAUDE database^[8] other studies revealed significantly varying fracture risk according to the brand of filter with the Celect filters having a very low fracture rate and the Bard Recovery filters having the highest as high as 25%^[9].

Fracture of a filter strut and intracardiac embolization^[10] has been reported in literature to be a devastating complication in some patients. An intracardiac strut can be asymptomatic as in our patient or present with a clinical picture similar to PE with shortness of breath, pleuritic chest pain, non-sustained ventricular tachycardia and life threatening cardiac tamponade. The use of IVC filter is trending up and the availability of various types with different risk profile mandates physicians to have knowledge regarding types of filters and clinical implications associated with each type to recognize the complications and institute timely appropriate management. The choice of filter should take into consideration individual risks of the filter, clinical indication for the filter and the required duration of treatment to avoid unnecessary complications.

Timely retrieval of retrievable filter can prevent the sequelae of fracture and embolization and the subsequent complications. In systematic review by Angel *et al.*^[11] the retrieval rate was as low as 34%. As a consequence of reported low retrieval rates the Food and Drug Administration in the United States has recommended that "the implanting physicians and clinicians responsible for the ongoing care of patients with retrievable IVC filters consider removing the filter as soon as protection is no longer needed"^[12].

Optimum management of intracardiac foreign bodies depends on the size and shape of the foreign body and the symptoms. Asymptomatic patients with a foreign body that is smoothly shaped and less than 5-10 mm can be managed conservatively. Our patient did not demonstrate any high risk features and thus was managed conservatively.

In conclusion, IVC filters are increasingly utilized in the clinical practice albeit with low retrieval rates of temporary filters which could result in potentially life threatening preventable complications. Timely retrieval of IVC filter is vital to prevent the unwanted sequelae associated with filter strut fracture and embolization. This case was written to highlight the importance of timely retrieval of filters and to enlighten physicians on rare complications associated with non-retrieval.

COMMENTS

Case characteristics

A 30-year-old African American male presented to the cardiology clinic for

cardiac risks stratification prior to renal transplant.

Clinical diagnosis

Physical examination was remarkable for scars in chest and extremities from prior burns treated with skin graft otherwise unremarkable.

Differential diagnosis

Foreign body in right atrium suspected either a fractured inferior vena cava (IVC) filter or a metal travelling intravascularly to heart following car accident.

Laboratory diagnosis

Unremarkable other than elevated creatinine due to end stage renal failure.

Imaging diagnosis

The transthoracic echocardiogram showed two linear echo bright densities in the right atrium and ventricle embedded in the wall. Non-contrast computed tomography of the chest confirmed the presence IVC filter was in place with the missing limbs evident on imaging.

Treatment

As patient was asymptomatic and the objects were found to be embedded in the myocardium vena cava filter retrieval was not advocated.

Related reports

Fracture of a filter strut and intracardiac embolization has been reported in very few case reports to be a devastating complication in some patients. However rates of IVC filter removal remains low.

Term explanation

IVC filters are used in patients with deep venous thrombosis of lower extremities with contraindications for anticoagulation's.

Experiences and lessons

Timely retrieval of IVC filter is vital to prevent the unwanted sequelae associated with filter strut fracture and embolization.

Peer-review

The authors describe an interesting and well documented complication of cava filter and give a nice review of literature.

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Ominous lung cavity "Tambourine sign"

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Institutional review board statement: Isolated case reports are exempt from review and approval at our institution.

Informed consent statement: Verbal informed consent was taken at the time of conducting investigations that the case may be used in academic and teaching purpose maintaining identity and confidentiality of the patient.

Conflict-of-interest statement: Nil.

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Abstract

Mucinous adenocarcinoma represents a rare subtype of adenocarcinoma of the lung, which is frequently invasive and has a poorer prognosis. Of its wide range of imaging appearances, air-space consolidation is the most frequent pattern while cavitary form has only rarely been reported. Despite imaging advancements, the differentiation of benign and malignant cavitary lung lesions sometimes remains imperfect. We propose "Tambourine" sign on computed tomography to raise the suspicion of mucinous adenocarcinoma in a lung cavity, under appropriate clinical settings. The sign indicates an irregular cavity with undistorted prominent thick walled bronchioles within the wall and draping along thereby resembling the musical instrument "tambourine". Adjacent ground glass and internal septations may also be seen.

Key words: Lung cavity; Tambourine; Adenocarcinoma mucinous; Tomography; X-ray

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Core tip: Lung cavities are commonly encountered in routine chest imaging and diagnosis may become a challenge in certain cases despite advances in imaging techniques. Imaging points have been described in literature to differentiate benign from malignant cavities that help in diagnosing most of the cases, however some lesions are still difficult to interpret and accurately diagnose. Tambourine sign has been introduced by us for a relative thin walled lung cavity where undistorted smaller bronchi with thickened and prominent walls are seen to be entering and draping along the cavity walls. This imaging sign resembles the musical instrument tambourine, and this is ominous and point towards a

more sinister lesion as in our case and in similar cases reported in literature. Hence in appropriate clinical and imaging background this sign should be carefully looked at and appropriate workup should be done for timely diagnosis.

Verma R, Bhalla AS, Goyal A, Jain D, Loganathan N, Guleria R. Ominous lung cavity “Tambourine sign”. *World J Clin Cases* 2017; 5(4): 153-158 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v5/i4/153.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v5.i4.153>

INTRODUCTION

Lung cancer is the most common cause of malignancy-related mortality in both sexes^[1]. In the recent decades, there has been a substantial increase in the proportion of adenocarcinomas, making it the most common type. The spectrum of lung adenocarcinoma ranges from atypical adenomatous hyperplasia to frankly invasive lesion^[2]. Invasive mucinous adenocarcinoma (IMAC) is a special subtype of adenocarcinoma lung that was earlier termed as mucinous broncho-alveolar carcinoma (BAC) and is known to be more aggressive than conventional adenocarcinoma^[3]. IMAC may have a wide range of imaging appearances, of which air-space consolidation is the most common^[2] pattern.

We present a case of 37-year female who presented with a thin-walled left lower lobe (LLL) lung cavity six years ago, but remained undiagnosed despite adequate workup, till a final diagnosis of IMAC was made. Review of literature focussing on radiological findings of this unusual cavitory appearance of IMAC is discussed.

CASE REPORT

A 37-year non-smoker female presented to our institute with history of cough, sputum, shortness of breath, loss of weight and episodic hemoptysis in November 2014. Her problem began in 2008 with an episode of cough, streaky hemoptysis and copious sputum production, which was treated with antibiotics as respiratory tract infection. Multiple subsequent hospital admissions and extensive clinical/radiological workup was done (Figure 1) for similar complaints but was inconclusive (Figures 2 and 3).

The laboratory investigations in the current admission were again non-contributory (Figure 1). Contrast-enhanced computed tomography (CECT) was done and it revealed multiple cavitory lesions in bilateral lungs with the largest in LLL showing large enhancing solid component. Many of the cavitory lesions in current CT showed a peculiar imaging appearance: Irregular inner and outer walls with thick walled bronchioles seen near the edge and within the walls of the cavities. No surrounding ground glass opacity (GGO) was seen in the current CT. There was no pleural effusion or mediastinal

adenopathy. The included sections of upper abdomen were unremarkable.

Review of the prior imaging (Figures 2 and 3) demonstrated progression over the last six years. The lesion began (in 2008) as a thin-walled (4 mm) well-defined cavity in superior segment of LLL (Figure 2A-C). Both the inner and outer margins of the wall showed irregularity. Adjacent thick walled prominent undistorted bronchioles (dotted arrows) were seen near the edge and within the wall of cavity. Mild surrounding GGO was also seen. There was an additional smaller cavitating nodule in right upper lobe (RUL) with subtle surrounding GGO (not shown). Combining clinical and laboratory data, patient was presumed to have respiratory infection and treated for the same. Subsequent imaging in 2010 (Figure 2D-F) showed increase in size and wall thickness of the LLL cavity. Imaging done in 2012 depicted multiple new cavitating nodules in RUL (Figure 3A and B) and increase in size of LLL cavity, along with development of internal septations. No GGO or consolidation was seen and there was no solid component in any of these cavities.

Current CECT images showed further increase in the size of the lesions and development of significant soft tissue component in LLL cavity (Figure 3C-E). Many of the cavitory lesions in the current CT showed multiple internal septations. Considering disease progression and development of solid component, malignancy was kept as the first differential. Other possibilities included atypical infections (fungal, atypical mycobacterial, nocardia, etc.) and vasculitis. However, long disease course (approximately 6 years) was unusual for both infection and malignancy.

USG-guided biopsy was done from the LLL mass (solid component) that showed atypical glands in the background of abundant mucin with areas of frank invasion suggestive of well-differentiated IMAC (Figure 4A and B). Analysis for ALK and EGFR mutation was negative. 18F-FDG PET-CT was done to rule out lung metastasis from extrathoracic primary which did not reveal any other primary site and the lung lesions showed patchy foci of mild FDG uptake (Figure 4C). The patient was started on chemotherapy (Pemetrexed and Carboplatin) but she continued to progress and developed bone metastases and soon became bed-ridden.

DISCUSSION

Lung cavities are commonly encountered in routine radiology practice. While in most cases the distinction between benign and malignant cavities is straightforward, some of the lesions may pose a diagnostic challenge. Differential diagnosis of acquired cavitory lung lesions include pyogenic infections such as lung abscess, necrotising pneumonia, septic emboli; granulomatous infections like tuberculosis, fungal; vasculitis including granulomatosis with polyangiitis (Wegener's) and Churg Strauss; connective tissue diseases like rheumatoid disease, ruptured hydatid and malignancy. A constellation of imaging features including wall thickness, number of lesions, distribution/site,

Clinical workup	Management
<p>2008: Figure 1</p> <p>Blood counts, sputum for AFB, fungal elements, Connective tissue and vasculitis workup^a, ACE, hydatid serology and ESR was normal</p> <p>↓</p> <p>2010: Figure 1</p> <p>Repeat blood work up[®] inconclusive; sputum that showed heavy growth of <i>S. viridans</i> but negative for AFB, fungal, atypical mycobacteria and nocardia. PFT: Normal</p> <p>↓</p> <p>2012: Figure 2</p> <p>Repeat work up inconclusive, Multiple BAL and FOB: Negative. CT showed progression. ECHO: Normal LV function, no vegetations. TBLB: Chronic inflammatory cells with some fibrosis</p> <p>↓</p> <p>2014: Figure 2</p> <p>Laboratory and clinical workup negative. USG guided biopsy from LLL solid component done s/o IMAC</p>	<p>→ Treated as respiratory tract infection, cavity was considered post infective</p> <p>→ Treated with antibiotics as superadded streptococcal infection</p> <p>→ Given empirical ATT, no response. Later itraconazole and steroids were added with some benefit. After that patient was on routine usage of inhaled steroids (formoterol + budesonide) with only occasional cough dyspnoea and chest discomfort. Advised LLL lobectomy but refused</p> <p>→ Started on Pemetrexed and Carboplatin</p>
<p>^a(ANA profile, dsDNA, Nucleosomes, Anti Histones, Ribosomal-P, p and c-ANCA), <i>etc.</i></p> <p>[®]Haemogram, ESR, KFT, LFT, sputum, galactomannin, HIV blood sugar, <i>etc.</i></p>	

Figure 1 The clinical work-up and evaluation from onset till diagnosis. BAL: Bronchoalveolar lavage; TBLB: Transbronchial lung biopsy; ACE: Angiotensin converting enzyme; EGFR: Epidermal derived growth factor receptor; PFT: Pulmonary function test; AFB: Acid fast bacilli; ESR: Erythrocyte sedimentation rate; GGO: Ground glass opacity; ATT: Anti tubercular therapy.

adjacent GGO/nodules/consolidation, satellite lesions, internal contents, fluid level and the background lung need to be considered to reach a diagnosis.

Amongst lung malignancies, squamous cell carcinoma is the most common type to present as cavitory mass while adenocarcinomas rarely show true cavitation due to lack of frank necrosis and relative preservation of lung architecture. Adenocarcinomas however show areas of pseudocavitation due to presence of air in the patent smaller bronchi and preserved intra-alveolar air^[4]. IMAC is a special subtype of invasive adenocarcinoma lung that is more common in females, non-smokers and presents at a younger age. When these tumors are multifocal, they are frequently multilobar and lower lobe predominance is seen^[2,5].

On CT, IMAC usually appear as consolidation with air bronchogram (commonest) or multifocal solid and subsolid (ground glass) nodules or masses which tend to be bronchocentric^[2,6]. Due to abundant mucin production, large areas of pseudocavitation may be seen. They have low FDG uptake^[7] due to large amount of mucin and for same reason show less contrast enhancement frequently depicting the “CT angiogram sign”.

Previously IMAC was termed as Mucinous Bronchoalveolar Carcinoma however the term BAC has now been

removed from recent adenocarcinoma classification. BAC by definition was for non-invasive tumors while IMAC though predominantly show lepidic spread, frequently have areas of frank invasion. GGO is an indicator of lepidic spread while the solid component correlates with invasion. IMAC are frequently EGFR negative and may show *k-RAS* mutation, therefore having a poorer prognosis^[8].

IMAC presenting as cavity is rare and to the best of our knowledge only two cases have been described previously^[9,10]. Cavitation in adenocarcinoma may be caused by obstruction of the distal bronchus by tumour cells creating a check-valve mechanism or alveolar rupture due to tumour proliferation or mucus retention^[9]. A detailed review of the previously reported cases and all the imaging studies of our case enabled us to come up with a peculiar finding common to all, which we intend to refer to as the “Tambourine sign”.

“Tambourine” sign refers to an irregular cavitory lesion with adjacent thick walled undistorted bronchioles within wall of the lesion and adjacent to it. The appearance resembles the musical instrument tambourine where the irregular cavity wall corresponds to the ring of the instrument, while the thick walled dilated bronchioles within the wall correspond to the metallic jingles. The cavity wall itself though irregular, may not be thick (as in

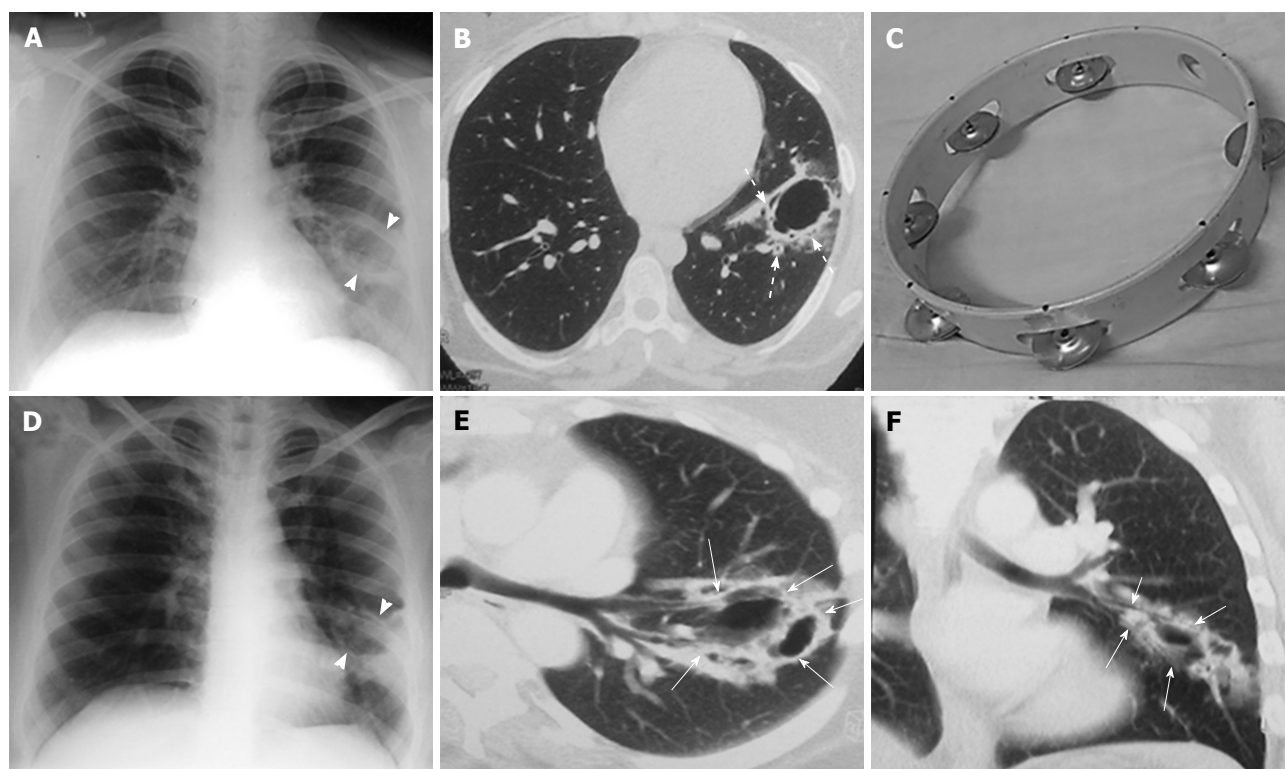


Figure 2 Initial and two year follow-up computed tomography imaging. Chest radiograph (A) and CT (B) in 2008 (first study) show well-defined thin-walled (4 mm) irregular cavitory lesion (arrow head) in superior segment of left lower lobe. Thick walled bronchioles (dotted arrows) are seen near the edge and within the wall of cavity with adjacent ground glass giving rise to "Tambourine" sign; (C) depicts the musical instrument "tambourine" for comparison; subsequent radiograph (D) and CT (E and F) in 2010 shows increase in size and wall thickness of the cavity. Note the adjacent bronchioles (thin white arrows) entering into the cavity wall. CT: Computed tomography.

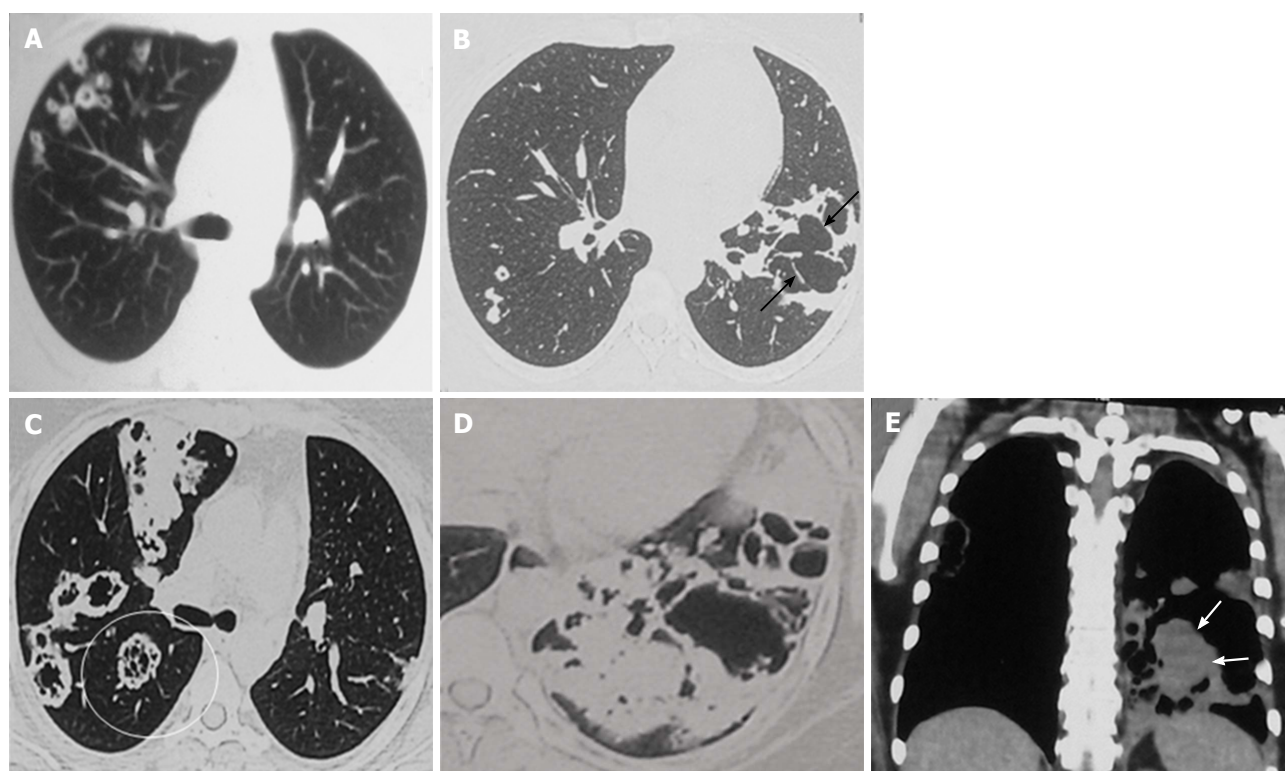


Figure 3 Disease progression with development of soft tissue. Chest CT study of 2012 lung window (A and B) shows multiple new cavitating nodules in RUL (A) and increase in size of LLL cavity with development of internal septations (arrows) (B). No solid nodules or GGO or consolidation is seen. Current CECT images (2014: C to E) demonstrate further increase in size of the lesions and multiple new lesions having internal septations and development of significant soft tissue component in LLL cavity (solid arrows). Also note the "Tambourine" sign in RLL cavities as well (encircled cavity in C). LLL: Left lower lobe; RUL: Right upper lobe; GGO: Ground glass opacity; CECT: Contrast-enhanced computed tomography.

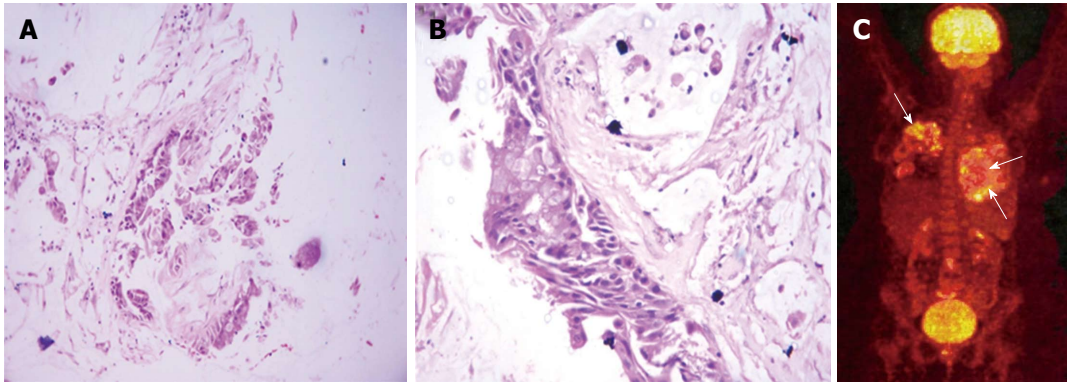


Figure 4 Histopathology and positron emission tomography findings. A and B: Histological photomicrograph shows fragments of tumor with mucinous epithelium H and E $\times 40$. Higher magnification (C) shows invasive mucinous adenocarcinoma with pools of extracellular mucin H and E $\times 400$; C: Whole-body PET-CT image shows patchy mild uptake of FDG within the lung lesions. No evidence of extrathoracic primary site of malignancy is there. PET-CT: Positron emission tomography-computed tomography; FDG: 2-[fluorine-18] fluoro-2-deoxy-D-glucose.

Table 1 Confounding factors leading to delay in diagnosis in the index case

Young age of presentation
Lack of significant soft tissue component and thin walls initially
Multifocality favoured a systemic infection/disease (vasculitis) rather than primary lung malignancy
Increase in wall thickness in second CT was suspicious, but interpretation was confounded by heavy growth of streptococcus.
Waxing and waning symptoms.
Repeated negative BAL and FOB

CT: Computed tomography; BAL: Bronchoalveolar lavage; FOB: Fiberoptic bronchoscopy.

the initial CT in the index case). Prominent thick walled undistorted bronchi are caused by tumour cell infiltration and desmoplastic reaction. Presence of internal septations and surrounding GGO (indicating lepidic spread of the tumor) further increase the likelihood of malignancy in such a lesion. When viewed in retrospect, both of the previously described cases as well as our patient showed “Tambourine” sign in all the CT examinations.

Paucity of malignant cells in such large amount of mucin^[11] may make IMAC difficult to detect on BAL cytology as well as on TBLB. Though adenocarcinomas are usually aggressive, unusually slow growing lesions have also been reported^[12,13]. This along with other confounding factors (Table 1) delayed the diagnosis in the index case. Adenocarcinoma may develop in a pre-existing cavity; however the index case was likely to be harbouring malignancy right from the onset. This is because the LLL cavity showed suspicious features on the first CT itself (tambourine sign) and progressively increased in size and wall thickness on subsequent imaging, along with development of multifocal lesions. The unusual feature in our case was atypical radiological appearance of the lesion as a thin-walled cavity, repeated negative cytology/biopsy and unusual slow growth.

Summary and conclusion

The purpose of this article is to highlight an additional

Table 2 Learning points

IMAC is more common in non-smokers and females and has poor prognosis
It has lower lobe predominance and is frequently multifocal
IMAC may be missed on repeated cytology and biopsies due to relative paucity of malignant cells and large amount of mucin
“Tambourine” sign in appropriate clinical setting identifies lung cavity suspicious for malignancy, especially IMAC
IMAC may show unusual slow growth and only mild uptake on PET

IMAC: Invasive mucinous adenocarcinoma; PET: Positron emission tomography.

radiological sign which could raise suspicion of malignancy in a lung cavity. An irregular cavitory lesion with adjacent thick walled undistorted bronchioles within wall of the lesion and adjacent to it (“Tambourine” sign) is suspicious for malignancy and needs extensive work-up even if the cavity is relatively thin walled. Internal septations, surrounding GGO, lower lobe location, multifocality, normal background lung without any obvious airway disease, fibrosis and scarring may further point towards underlying malignancy (IMAC), provided the work-up for other differentials is negative (as in our case). Any increase in size or wall thickness prompts aggressive management by early surgical removal even when repeated BAL or biopsy is negative (Table 2).

COMMENTS

Case characteristics

Cough, shortness of breath and occasional hemoptysis.

Clinical diagnosis

Respiratory tract infection.

Differential diagnosis

Reactivated kochs.

Laboratory diagnosis

Was confusing and non contributory.

Imaging diagnosis

Initially lung cavity with tambourine sign initially later developed soft tissue.

Pathological diagnosis

Invasive mucinous adenocarcinoma.

Treatment

Premetrexed and carboplatin combination chemotherapy and radiotherapy for bone metastasis.

Related reports

Being thin walled cavity with no significant soft tissue repeat biopsies may be negative hence surgical excision may be considered when extensive workup is inconclusive.

Term explanation

The cavity resembles “Tambourine” on computed tomography, that refers to the musical instrument seen as thin walled cavity in background of normal lung with prominent and thick walled undistorted bronchi draping and entering the cavity walls.

Experience and lesson

This imaging finding has been retrospectively observed in previous similar reported cases of Invasive mucinous adenocarcinoma presenting as cavity and hence the classical appearance need to be focussed and re-emphasised. Close follow-up is very helpful in such cases.

Peer-review

Nice case and also well drafted.

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