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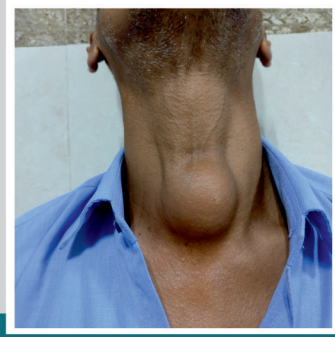

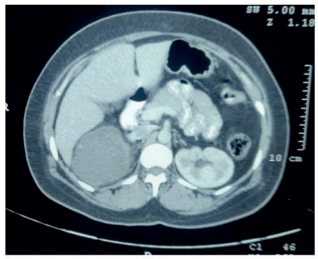

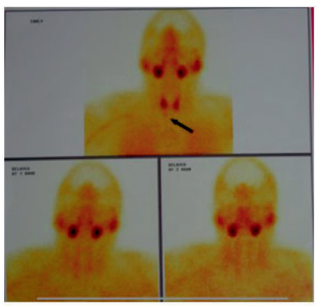

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Aims and Scope

IAES, a section of ASI was started in the year 1993 by Padmashri Prof. S. Vittal as its founder president. The Association has evolved into a vibrant organisation is one of the best performing sections of ASI. The association has been a pillar of strength in the development of Department of Endocrine Surgery in Madras Medical College, SGPGIMS, Lucknow, KGMU, Lucknow, AIIMS, New Delhi, AIIMS, Patna and CMC, Vellore. The Association takes pride in the dissemination of Principles and practice of Endocrine Surgery to all Surgeons. It conducts CME Programmes, Organises Annual Meetings and awards Fellowship (FAES) as part of its initiative to update its member and to popularise Endocrine

Surgery amongst the Surgeons.

The aim of Indian Journal of Endocrine Surgery is to promote and encourage development and advancement of Endocrine Surgery and allied specialties. It focuses on encouraging and promoting clinical and research activities pertaining to Endocrine Surgery. It plans to bring in concept of multi disciplinary team approach in management of various endocrine pathology. The journal publishes original articles, review articles and case reports.

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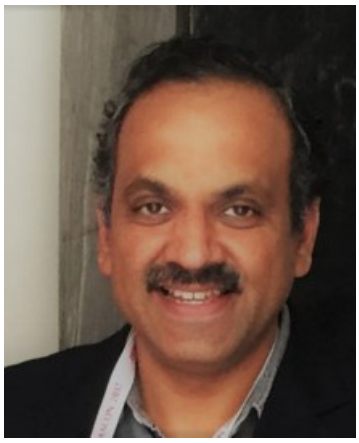
From the Editor's Desk



Dear IAES Members,

It has been an eventful year of the Covid pandemic with all its challenges and we have adapted well on the virtual platforms. It is with great pleasure I bring out this issue of Annals of Endocrine Surgery which carries articles contributed by our dear members. It is certainly an important part of our functioning as an association of professionals to share from our work and research. In today's world of social media, instant communication is the norm, but will nicely complement the due diligence required to sit and write out scientific matter thoughtfully. I specifically encourage members from the smaller hospitals to share the challenges of practicing in resource constrained settings and the innovations you make for others to learn.

I am thankful to those who have contributed articles, the office bearers of the association particularly to the members of editorial board and my secretary for helping in bringing out this issue.

I am glad to hand over to Pooja Ramakant, who will spearhead our effort to start an indexed journal for the association. I encourage all endocrine surgical departments and surgeons to support this venture.

Prof. M J Paul, *MS, DNB, FIMSA, FRCS (Glasg)*
Professor and Head, Department of Endocrine Surgery
Assoc. Director, HR
Christian Medical College Hospital, Vellore, Tamilnadu 632004. INDIA
Tel: 0416 228 3054 (O), 4388 (R)
Mobile: 9486660601
Email. mjpaul@cmcvellore.ac.in

From the President

Dear Esteemed Members

Season's Greetings on behalf of IAES Executive Committee. I must thank Editor in Chief, Dr M J Paul and his Editorial team for bringing out another edition of Indian Journal of Endocrine Surgery. We are amidst trying and testing times due to the pandemic. I hope all of you are taking appropriate precautions during the discharge of your professional work. On a personal note I feel honoured and privileged to have lead this august association following in the footsteps of my father Dr S Vittal, the Founder President of this Association. I am an ardent admirer of him for his infectious enthusiasm and his passion for teaching.

This Journal is an important tool for dissemination of Principles and Practice of Endocrine Surgery to all our colleagues especially our Fellow IAES members. The core aim is to encourage and promote clinical and research activities pertaining to Endocrine Surgery and allied specialties. I am confident that this journal will raise to greater heights under the leadership of my illustrious successor Dr M J Paul. Once again I am thankful to the entire Editorial team for bringing out this edition and wishing the esteemed members for a Happy, Healthy and Prosperous 2021!

Stay Safe!

Best wishes

Dr Sai Krishna Vittal
President IAES

From the Honorary Secretary

I am very happy to know that Indian Association of Endocrine Surgeons is bringing out the journal under the able leadership of President Dr Sai Vittal. It is very heartening to know that the new issue will be launched this week only when we have our sectional meeting at the Annual conference of Association of Surgeons of India. During this pandemic everyday as we are discovering 'new normal', the conference is totally virtual.

The richness of the association is known by academic activities which is reflected by faculty deliberations, participation of members and their publications. Journal of own association always gives lot of pride and happiness.

To bring out the journal is not an easy task and it needs very hard work, vision and team work. As an Executive member of the national body and Vice President of the association I congratulate Dr. M J Paul Editor in chief and whole editorial editorial team for bringing out the issue of Indian Journal of Endocrine Surgery.

As we are in the third phase of pandemic and inching towards the vaccine I wish and pray to keep all my colleagues, members and their family members safe and healthy. I wish all my friends in executive committee and members 'Merry Christmas' and a very 'Happy New Year 2021'.

Long live IAES….

Anand K. Mishra
Professor and Head
Department of Endocrine surgery
King George's Medical University
Lucknow-226003

Organizing Secretary PINK MARATHON 2018
www.pinkhalfmarathonlucknow.com
IDEA award, American society of clinical oncology 2011
International Guest Scholar, American college of Surgeons, 2015
Hon. Secretary, Indian Association of Endocrine Surgeons
Executive Member, Indian Association of Breast Surgeons
International advisor, Asian Association of Endocrine Surgeons
Ph: 919415007391

Sir Richard Owen – Discovery of Parathyroids

Kaushik Bhattacharya MS DNB MNAMS FAIS FACS FRCS (Glasgow)
Specialist Surgery
CAPFs Composite Hospital BSF Kadamtala
Siliguri, West Bengal , India
Address for Correspondence- Dr. Kaushik Bhattacharya, G616, Uttorayon, Matigara, Siliguri 734010
West Bengal, India, Email kbhattacharya10@yahoo.com

Owen: the most distinguished vertebrate zoologist and palaeontologist... but a most deceitful and odious man."

— Richard Broke Freeman in Charles Darwin: a Companion, 1978

In May 1834 the Zoological Society of London purchased its first Great Indian Rhinoceros (Rhinoceros unicornis), which died on the evening of 19th November 1849, its carcass was offered to Sir Richard Owen (1804–1892), Hunterian Professor and Conservator of the Museum in the Royal College of Surgeons of England . Owen welcomed the 'rare opportunity', and the dissection took place in the winter months of 1849 to 1850 at the Conservator's resident quarters. The animal weighed about 2 tons and by the time Owen's work was completed it was in an 'offensive state of decomposition'. His account of the dissection, published in 1862, includes the rhinoceros's last days as recorded in the Head-Keeper's minute book: it had vomited 'slimy mucus with blood' for a week before succumbing. Owen found that a fractured rib had punctured the animal's lung on the left side and concluded that this was the likely cause of death [1].

In his detailed description of the anatomy, Owen refers to 'a small compact yellow glandular body attached to the thyroid at the point where the vein emerged'—a structure we now know as the parathyroid gland. The original preparation in which Owen made the observation is still to be seen in the Hunterian Museum at the College. It measures 30×14×8 cm and consists of part of the larynx and trachea of the rhinoceros, showing the lateral lobe of the thyroid with a parathyroid attached to its upper extremity and partly embedded in its substance .

He published his work as the third article in the fourth volume of the Society's Transactions, not in 1862 as commonly believed, but ten years earlier, in March 1852. It was Professor AJE Cave, successor to Owen as Professor of Anatomy at the RCS, who noted that Owen's paper had been published in 1852 and not in 1862 as originally thought. To honor Owen's achievement, Cave in 1953 conferred on these glands the term "glands of Owen" [2]..

Richard Owen was born on July 20, 1804, in Lancaster, where he was apprenticed to a local surgeon in 1820. He studied medicine at the University of Edinburgh from 1824, completing his medical studies at St. Bartholomew's Hospital, London. His interest in anatomy led to his appointment in 1827 as assistant curator of the Hunterian Collection of the College of Surgeons in London. In 1831 he went to Paris to attend the lectures of Baron Cuvier, regarded as the world's foremost authority on comparative anatomy.

Owen's 1832 "Memoir on the Pearly Nautilus" established his reputation as an anatomist and was largely responsible for his election as a fellow of the Royal Society in 1834. Owen remained at the College of Surgeons until 1856, being appointed. Hunterian professor of comparative anatomy and physiology in 1836.

Owen was also a taxonomist, naming and describing a vast number of living and fossil vertebrates. As a prosector for the London zoo, he had to dissect and preserve any zoo animal that died in captivity. It also caused him some domestic difficulties, as he had to do this work at his own house, his wife Caroline recorded in her diary how, one summer day , " the presence of a portion of the defunct elephant on the premises rendered the house so foul smelling that

she got Richard Owen to smoke cigars all over the house".

He developed a reputation for controversy, was accused of stealing other scientists' specimens and undermining people by writing anonymous reviews of their work, while supporting them in public. Owen's contemporary and rival Gideon Mantell described him as "overpaid, over-praised and cursed with a jealous monopolising spirit".

Sir Richard Owen , scientific founder of the Natural History Museum, devoted opponent of materialistic transmutation and natural selection, and said to be the only man that Darwin ever hated, was almost lost to the history of science before his death, although in his time he was the most influential of British biologists. Owen gave us the name Dinosauria and dozens of others, and he established for Anglophonic biologists the classification of mammals, standardized the terminology of teeth and the names of the skull bones, and distinguished between homology and analogy. He was the first to describe the newly discovered pearly nautilus, a "living fossil," and he made as many contributions to the anatomy and relationships of extinct vertebrates as to living ones-approximately 800 papers, books, and monographs, spread over 60 years. When Owen commissioned from artist Benjamin Waterhouse Hawkins the first dinosaur model, the top was kept open and a dining table set up inside. And in true Victorian style a grand New Year's Eve feast was served to Owens and his colleagues inside this new dinosaur creature. Just imagine feasting inside the giant model of an animal that was previously unknown to humanity!

Owen was an astute politician, and soon came to be admired by the key figures in British natural history, which at the time was primarily an Oxbridge-based, Anglican clique. Indeed, his reputation spread to such an extent that Prince Albert eventually asked him to tutor the royal children. The prince also suggested Owen be put in charge of designing the dinosaur exhibits for the Great Exhibition of 1851. Owen was awarded the Copley medal in 1851, the Linnaean medal in 1888, and knighted in 1873, and it was primarily because of his vision and efforts that London's Natural History Museum was established.

Charles Darwin finally commented " I used to be ashamed of hating him so much, but now I will carefully cherish my hatred and contempt to the last days of my life". Sir Richard Owen died at Richmond on December 18th, 1892. Tall in stature, ungainly in figure , with a massive head, lofty forehead, high cheek bones, large mouth, long lark hair, florid complexion, and prominent expressive eyes, he possessed an affectionate nature and an engaging manner, and was a delightful conversationalist. [3]

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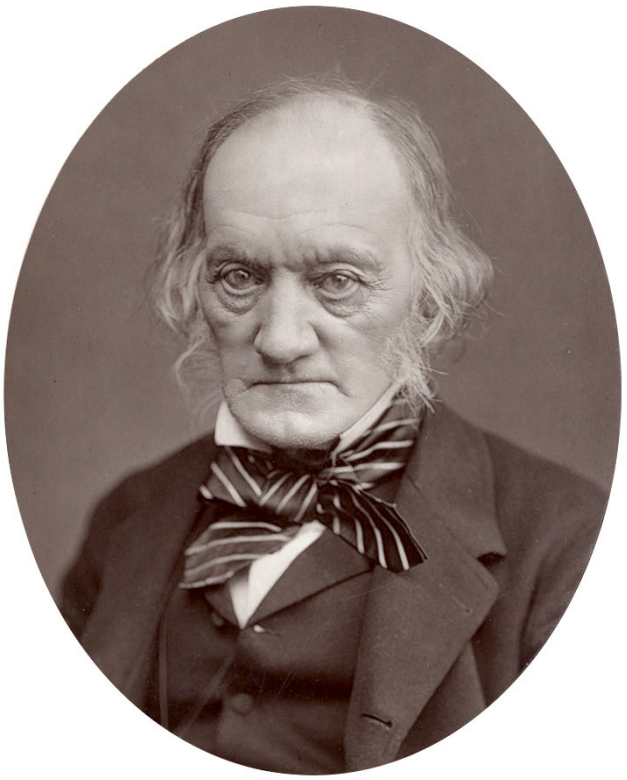


Figure 1....Sir Richard Owen (1804–1892)

ORIGINAL ARTICLE

Clinical assessment of the thyroid nodule: Factors that predict malignancy – A Prospective study

Vimalin Samuel, Paul M Jacob,
Endocrine Surgery, CMC Vellore

Keywords: Thyroid, malignancy, nodule

INTRODUCTION:

Thyroid nodules are found in around five percent of the adult population with an increase in incidence if ultrasonography is used as a screening tool; between 5%–15% of these nodules will be malignant depending upon age, gender, radiation exposure history, family history and other factors.(1)

Differentiated thyroid cancer (DTC), which includes papillary and follicular cancer, comprise the vast majority (90%) of all thyroid cancers. The increasing level of detection may be due to the increasing patient awareness, more frequent use of neck ultrasonography and incidental detection in other imaging modalities. The evaluation of a patient with a thyroid nodule consists of three arms; a good history and physical examination, ultrasonography of the gland and fine needle aspiration cytology of the nodule apart from biochemical assessment of function; yet 30-40% of nodules remain undiagnosed. Identifying the thyroid nodule that is malignant and requires surgical excision is a challenge to the surgeon.

Most of the literature and guidelines that are available have been based on studies that been conducted on western population. Does the same hold good for the Indian population?

METHODS:

All patients presenting with newly diagnosed nodule/s of thyroid were included in this study. The clinical assessment was done by a two senior consultants. Most ultrasonograms were done before FNAC, by the designated radiologist. Ultra sound guided FNACs were done if the clinicians felt it was required.

The cytology was reported as per the Bethesda criteria. The gold standard for diagnosis in this study was taken as the histopathology result. The study was conducted in the time period between May 2011 and June 2012. There were 102 cases with malignant histopathology versus 93 cases of benign histopathology.

The following clinical criteria were used to indicate increased risk of malignancy:

- Age >40 YRS
- Male gender
- Family history of thyroid malignancy
- Persistent dysphonia, dysphagia or cough
- Consistency - hard
- Fixed swelling

Statistics:

The information was entered into Epi Data and analysed using SPSS after conversion to an excel spreadsheet

Literature review:

CLINICAL EVALUATION OF THYROID NODULES:

History and clinical examination:

There is no doubt that first and foremost, for an evaluation of a thyroid nodule, a detailed history and thorough clinical examination will lead the way to a sound diagnosis. Patients usually present with a large palpable nodule in the neck incidental nodule found on imaging studies . Some palpable nodules may not correspond to radiological abnormalities. Non palpable nodules that are detected on ultra sound or other anatomic imaging studies, usually as part of evaluation for other reasons are called incidentally discovered nodules or ''incidentalomas''. Non palpable nodules have a similar risk of malignancy as palpable nodules that are of the same size(2).

Generally, only the nodules that are >1 cm in size should be evaluated, as they have significantly higher risks of malignancy(2).

There are some nodules which are <1 cm in size that may require complete evaluation when suspicious ultra sound features, associated palpable lymphadenopathy or previous history of radiation to head or neck or history of thyroid malignancy in first-degree relatives(2).

However, in a recent study by Burch HB, Shrestha M, Crothers BA, they analysed Whether the size of the nodule plays a role in predicting malignancy.

During a ten year period (2001 to 2011), 3013 patients had fine needle aspirations of thyroid nodules at the Walter Reed Army Medical Center(3). The patients who underwent subsequent thyroid surgery were included in the analysis(3). The nodule size was assessed by ultrasound measurement of the largest diameter and cate¬gorized as 0.5 to 0.9 cm (group A), 1.0 to 3.9 cm (group B) and ≥4 cm (group C)(3). FNA cytology was categorized by the Bethesda System for Reporting Thyroid Cytopathology: benign, atypia (follicular lesion of undetermined significance), follicular neoplasm, suspicious for malignancy, or malignant. All categories except for benign were considered positive for calculation of the sensitivity and speci¬ficity of the FNA. There were 35 nodules in group A, 533 nodules in group B and 127 nodules in group C. The malignancy rate based on surgical pathology was 18.6% (129 of 695 nodules) and did not differ among the size categories. The malignancy rate was 23% in both men and women. (3) So this leads us back to the question of whether size matters? Traditionally, the teaching has been that, nodules greater than 4cm are at high risk for malignancy. However with the advent of imaging and detection of smaller cancers, size does not appear to be a risk factor.

The most pronounced environmental risk factor for thyroid cancer is exposure to ionizing radiation. Ionizing radiation is either due to medical treatment (childhood radiation therapy for benign or malignant disease, adult treatment of malignancies) or nuclear fallout (atomic bomb / testing survivors, nuclear energy accidents).

Ionizing radiation may exert this effect through several changes to the cell, including Genomic instability. The effects of ionizing radiation are most pronounced in children,

Especially those younger than 10 years old at the time of exposure. The latency Period of developing cancer from this exposure is approximately 10 years for patients Having external beam radiation exposure to less than 5 years for victims of the Chernobyl accident and the increased risk persists for 30 to40 years. Exposure to Ionizing radiation has been shown to increase the risk of malignancy for a thyroid Nodule to 30% to 40%. Furthermore, this risk of malignancy is increased regardless of nodule number and size and multifocal malignancy is found more than half of the time. A history of prior radiation exposure mandates initial total thyroidectomy. The gender-specific distribution is equal in those older than 65 and given that overall two- thirds of cancer cases are women, there would seem to be a link between reproductive hormones and the development of thyroid cancer. Estrogen has been linked as a stimulus for genomic instability and this may be how it exerts its mutagenic effects on the thyroid. Studies have yet to conclusively link traditional carcinogens such as alcohol and tobacco to the development of well differentiated thyroid cancers. Data are conflicting as to what role iodine - rich versus iodine - deficient diets play in the development of thyroid cancer.

Countries with iodine-rich diets such as the United States and Sweden have slightly increased incidence of papillary cancer and countries with iodine-deficient diets such as Switzerland and Australia have slightly increased incidence of follicular thyroid cancer. (4) A dominant or solitary nodule is more likely to represent carcinoma than a Multi nodular gland with an incidence of malignancy from 2.7 to 30% and 1.4 to 10% respectively(1). Yet, the overall risk of malignancy within a gland with a solitary nodule is approximately equal to that of a multi nodular gland due to the additive risk of each nodule. Important elements in the patient's history which increase the likelihood of malignancy include reports of rapid growth, dysphagia, dysphonia, male gender, presentation at extremes of age (less than 20 years or more than 70 years) and a family history of medullary thyroid carcinoma or multiple endocrine neoplasia(1). Patients must be asked for any family history of either benign or malignant thyroid diseases. Although not well defined, there most certainly exists a genetic component to thyroid cancers. In fact a family history of thyroid carcinoma may increase an individual's risk 3-fold when a parent has the disease and up to 6-fold if a sibling has the disease.(4)

The familial medullary thyroid cancers, multiple endocrine neoplasia 2, The familial papillary thyroid

tumours, familial polyposis coli, Cowden disease, Gardner's syndrome even though they are not common, must be considered.(5). Papillary thyroid cancers and follicular thyroid cancers have distinct genomic and proteomic signatures. Pathways are now emerging that demonstrate how these differences play a role in governing tumor biology. Mutations that involve RET, NTRK1, BRAF, PPARγ, or Ras can be detected in almost 70% of cases. There are at least 12 different RET mutations, known as PTC/Ret chimeric onco proteins, which seem to be an early event in thyroid tumorigenesis, with series showing a high prevalence in papillary micro carcinomas and also a high proportion of the post-Chernobyl childhood-induced papillary thyroid carcinomas.

BRAF mutations are seldom found in radiation-induced cancer. These mutations are postulated to produce a more aggressive phenotype of papillary cancers as they are found in many of the more poorly differentiated subtypes. Follicular carcinomas have mutations in PPARγ (rarely found in papillary cancers), AKT pathways, and Ras. Symptoms like difficulty in breathing, neck tenderness, pain, difficulty in swallowing or even change in voice can be attributed to thyroid problems, but in many patients, these symptoms are due to non thyroid diseases. In those patients that are symptomatic, evaluation must start with getting a proper history, doing a full physical examination, reassuring the patient and for choosing the correct laboratory tests. Acute pain is most often because of hemorrhage in to a nodule that is cystic in nature. However, patients that present with rapid increase in size of the thyroid nodule, lymphoma or anaplastic carcinoma of thyroid must be considered.

The beginning and slow progress of neck symptoms and signs are usually because of compression of the structures in the neck and upper chest cavity (oesophagus and trachea), which happens in those thyroid nodules that are found in large goiters.

The features of compression are not so common and are found in the elderly or middle-aged having a long - standing multi nodular goitre. The goiter that is growing downwards into the superior mediastinum can result in partial or complete obstruction of the chest inlet, causing venous obstruction. When the patient is made to raise his or her arms above the head ; i.e. Pemberton's sign, more narrowing of the chest inlet is produced which is followed by over filling of the external jugular veins and facial congestion.

If this is seen when there is a smaller goiter, the features of tracheal compression may suggest an underlying cancer. Differentiated thyroid cancers will usually not cause airway obstruction or vocal cord palsy or oesophageal problems but even if there are no symptoms, it does not rule out malignancy.(5)

Physical examination:

Physical exam findings that increase the concern for malignancy include:

- Nodules that are larger than 4 cm in size (19.3% risk of malignancy)
- Firmness to palpation
- Fixation of the nodule to adjacent tissues
- Cervical lymphadenopathy

However, these findings are very often limited by certain factors such as the patient's body habitus, as well as an inherent variation between physicians and their assessment of nodules so much so that precise measurement using imaging is a must of evaluation of a thyroid nodule.(1)

A hard nodule is suspicious as traditionally goitre has always been described as firm. However a benign multi nodular goitre may turn hard because of calcifications or hemorrhage.

Fixity of a nodule is because of its infiltration into surrounding structures. This feature is seen in malignant thyroid nodules and fixed swelling almost always require excision.

Cervical lymphadenopathy in the Ipsilateral level 3 or 4 is the most specific pointer to malignancy in a thyroid nodule; rarely this may prove to be red herring as in a patient with a thyroid swelling, they may have associated reactive hyperplasia of a the corresponding draining lymph nodes especially in the presence of autoimmune thyroiditis. However, it is essential to assess these lymph nodes with an ultra sound of the neck and plan the surgery with an option of doing a neck dissection with a frozen section of the lymph node if necessary.

RESULTS:

Table 1 : Age distribution of cases					
			Cases		
			Malignant	benign	Total
Page	15 - 40	No.	64	35	99
		% within age	64.6%	35.4%	100.0%
	41-50	No.	22	33	55
		% within age	40.0%	60.0%	100.0%
	>51	No.	16	25	41
		% within age	39.0%	61.0%	100.0%
Total		No.	102	93	195
		% within age	52.3%	47.7%	100.0%

P value = 0.002

Table 2: Sex distribution					
			Cases		
			malignant	benign	Total
Sex	female	No.	69	64	133
		%	51.9%	48.1%	100.0%
	male	No.	33	29	62
		%	53.2%	46.8%	100.0%
Total		No.	102	93	195
		%	52.3%	47.7%	100.0%

P=0.861

Table 3 : Features of compression or nerve involvement					
			Cases		
			malignant	benign	Total
		Asymptomatic	85	76	161
		%	52.8%	47.2%	100.0%
		Symptomatic	17	17	34
		%	50.0%	50.0%	100.0%
Total		Count	102	93	195
		%	52.3%	47.7%	100.0%

P=0.767

Table 4: Dominant consistency					
Dominant consistency			cases		Total
			malignant	benign	
		Hard	11	1	12
		%	91.7%	8.3%	100.0%
		Soft	2	1	3
		%	66.7%	33.3%	100.0%
		Cystic	0	3	3
		%	.0%	100.0%	100.0%
		Firm	89	88	177
		%	50.3%	49.7%	100.0%
Total			102	93	195
		%	52.3%	47.7%	100.0%

P=0.01

Table 5: Fixity to surrounding structures					
			cases		Total
			malignant	benign	
fixity		No	98	93	191
		%	51.3%	48.7%	100.0%
		Yes	4	0	4
		%	100.0%	.0%	100.0%
Total		Count	102	93	195
		%	52.3%	47.7%	100.0%

P=0.054

Table 6: Clinical size					
Size in cms			Cases		Total
			malignant	benign	
size	0-3		46	33	79
		%	58.2%	41.8%	100.0%
	3-6		41	37	78
		%	52.6%	47.4%	100.0%
	>6	Count	15	23	38
		%	39.5%	60.5%	100.0%
Total		Count	102	93	195
		%	52.3%	47.7%	100.0%

P = 0.164

From Table 1, it is clear that most of our patients were in the age group 15 – 40 yrs. There were more number of benign thyroid swellings than malignant, which was statistically significant(P=0.002). However, literature tells us that malignant swellings are common in the younger and older extremes of age(9). This is not reflected here in this study. It could be because, there were lesser number of patients in the >50yrs age groups.

Table 2 shows us that there were more number of females enrolled into the study than males. But the number of benign and malignant thyroid swellings were almost equally distributed in the male group.

This is contrary to literature that tells us that being of male sex is a risk factor for malignancy(9).

Table 3 tells us that even though traditionally features of compression or nerve involvement have been considered as features of malignancy, it may not be the case.

Table 4,5 show us that hard consistency, fixity are definite risk factors for malignancy with a significant P values. Table 6 reveals that larger size was not a risk factor for malignancy.

DISCUSSION:

This study was conducted on a small sample size in a single centre with its own bias of patient profile; therefore extrapolation to a general population is limited. Previous similar studies have had a larger ample size. Most have been retrospective studies making it much easier to acquire a large sample size. However, this was a prospective study, over a period of one and a half years, therefore the data may be more reliable.

CONCLUSIONS:

This small prospective clinical study revealed some interesting clinical pointers to malignancy.

1) Older age and male gender were not risk factors for malignancy.

2) Features of compression was not a risk factor for malignancy.

3) Hard consistency, fixity were definite risk factors for malignancy.

4) Size was not seen to be a risk factor for malignancy in this study

The need for a larger community based study or a multicentre study of pooled data in further clarifying these clinical points of diagnosis in the Indian context is apparent.

REVIEW ARTICLE

Sub-centimetric recurrent and persistent metastatic lymph nodes in well-differentiated thyroid cancer: Operate or observe?

[1]Sanjeet Kumar Jaiswal, MBBS, MD, DM, [2]Sanjay Kumar Yadav, MBBS, MS, MCh, [3]Chandan Kumar Jha, MBBS, MS, MCh, [4]Ashutosh Silodia, MBBS, MS, [5]Arvind Baghel, MBBS, MS, [6]Nishtha Yadav, MBBS, MD, DM, [7]Goonj Johri, MBBS, MS, MCh

[1]Assistant Professor, Department of Endocrinology, Seth G.S. Medical College & KEM Hospital, Mumbai, India [2]Assistant Professor, [4]Professor, [5]Associate Professor, Department of Surgery, Netaji Subhash Chandra Bose Medical College, Jabalpur, Madhya Pradesh, India [3]Assitant Professor (Endocrine Surgery), Department of Surgery, AIIMS, Patna, India [6]Senior Resident, Department of Radiology, Netaji Subhash Chandra Bose Medical College, Jabalpur, Madhya Pradesh, India, [7] Assistant Professor, Department of Endocrine Surgery, KIMS, Bhubaneswar

Corresponding Author : Dr. S. K. Yadav, Assistant Professor, Dept. of Surgery, Netaji Subhash Chandra Bose Medical College, Jabalpur, Madhya Pradesh, India, E- Mail: sky1508@gmail.com

Abstract:

Differentiated thyroid carcinoma (DTC) constitutes > 90% of all thyroid cancers and is generally associated with a very good prognosis due to effective surgery and adjuvant therapies. The overall survival (OS) rate at 10 years is reported to be 80 to 94%. Despite an excellent prognosis, , locoregional recurrences are common and warrant lifelong follow up. Locoregional recurrence is a significant cause of morbidity among DTC patients. Various studies have reported that mortality in DTC patients is directly related to loco-regional recurrence. Optimal treatment for the management of recurrent/persistent lymph nodes in DTC is still debatable, especially for low volume disease. Modalities available for treatment are either surgery/ and RAI or observation. Local ablative therapies like alcohol ablation and radiofrequency ablation are also being used by various groups. The contentious issue is recurrences of less than one centimeter. Follow up with Tg/ATg and USG neck is a reasonable alternative to surgery as finding subcentimetric lymph node in scarred tissue is particularly difficult even in expert hands.

Keywords: Differentiated thyroid cancer, Metastatic lymph node, lymph node dissection, recurrent lymph node, persistent lymph node

Core tip: There are several reviews in the literature on the management of persistent or recurrent central/ lateral compartment lymph nodes in a follow-up patient of differentiated thyroid carcinoma. However optimal management of sub-centimetric recurrent/ persistent lymph nodes is still debatable due to lack of randomized controlled trials. In this mini-review, we have tried to summarize the most appropriate management strategy based on currently available literature.

Introduction:

Thyroid carcinoma is the most common endocrine malignancy [1]. Differentiated thyroid carcinoma (DTC) is the most common entity comprising > 90% of all thyroid cancers[2]. DTC has generally a very good prognosis due to effective surgery and radioactive iodine therapy [3]. Overall survival (OS) rate at 10 years in both low-risk and high- risk groups of papillary thyroid carcinoma (PTC) has been reported to be 94 and 62% respectively[3,4]. The OS is somewhat lower for folliculat thyroid cancers (FTC) but still is 80 and 54% for low and high risk groups respectively. Mazafferri et al. have reported long term recurrence rates of DTC patients [5]. 40-yr recurrence rates were about 35%, two-thirds of which occurred within the first decade after initial therapy. Local (or locoregional?)disease comprised 68% of

the recurrences in their study and the 30-yr cancer mortality rate was twice as high with recurrence in the neck soft tissues (30%) compared with those in cervical lymph nodes or the contralateral thyroid (16%) [5]. The overall recurrence rate was reported to be 26% by Shaha et al [6]. The overall local, regional, and distant recurrences were 10%, 13%, and 13%, respectively. Recently Kim et al.[7] from Korea reviewed the recurrence pattern in 2250 patients with PTC larger than 1 cm who achieved complete remission after total thyroidectomy and/or radioactive iodine treatment. During 8.1 years of mean follow-up, 68 (3.0%) patients developed structural recurrences: 53 lymph node recurrences (LNR), 11 local soft tissue recurrences (LR), and 4 distant recurrences (DR). Locoregional recurrence was most common in 70.9%, distant in 16.5%, and both sites in 12.7% of patients with DTC recurrence in a study by Anjali Mishra et al. [8]. Various studies have reported that mortality in DTC patients is directly related to locoregional recurrence[9,10,11,12].

As we can see, locoregional recurrence is a significant cause of morbidity among DTC patients. The management of larger lymph node recurrences (>8-10 mm) is more or less standardized but the management of sub-centimetric central compartment lymph node(CCLN) and/or lateral compartment lymph node(LCLN) is contentious with a number of available therapeutic options, including observation. In this mini-review, we present an optimal management strategy based on currently available literature.

Predicting the recurrence:

AJCC staging system does not predict the risk of recurrence accurately. The overall recurrence rate in AJCC stage II is higher than AJCC stage III, 51% and 37% respectively[4]. American thyroid association's initial risk stratification system is more accurate in predicting recurrence. The rate of recurrence is 14% for low risk, 44% for intermediate-risk and 87% for high risk[13]. Apart from this, older age (>45 years), larger tumor (>2-4 cm), extrathyroidal extension, cervical node metastases, especially if extensive, distant (extracervical) metastases, aggressive histological subtypes (tall cell, insular, columnar cell, Hürthle cell carcinoma, follicular thyroid cancer and hobnail variant) and presence of BRAF mutation are associated with higher recurrence rates[14,15].

Diagnosis of Lymph Node Recurrence:

ATA guidelines for the management of DTC recommends that thyroglobulin (Tg) should be measured every 6-12 months by an immunometric assay and ideally in the same lab, the same assay along with ATg antibodies [16]. Hyperthyroglobulinemia after initial treatment (surgery with or without RAI) is generally an indication of recurrent thyroid cancer. High-resolution ultrasonography of the neck (HRUSG Neck) is the most sensitive radiological investigation for anatomical evaluation of regional LN and the thyroid bed. High resolution 7.5-10 MHz transducer can detect tumor deposits of as small as 2 mm in bed and lymph nodes (LN) [17]. Any lymph node of size more than 7mm in shortest diameter with hyperechoic punctuations or microcalcifications in context of of DTC should be considered metastatic because they seldom exist in metastatic LNs from other cancers [17].Functional scanning with I-131 or I-123 is another option. With oral use of 2-5 mCi of I-131, the neck can be visualized in 24 hrs [18].

Cross-sectional imaging of the neck and upper chest (CT, MRI) with IV contrast should be considered if bulky and widely distributed recurrent nodal disease, potential aerodigestive tract invasion, when neck US is felt to be inadequately visualizing possible neck nodal disease (high Tg, negative neck US)[16].

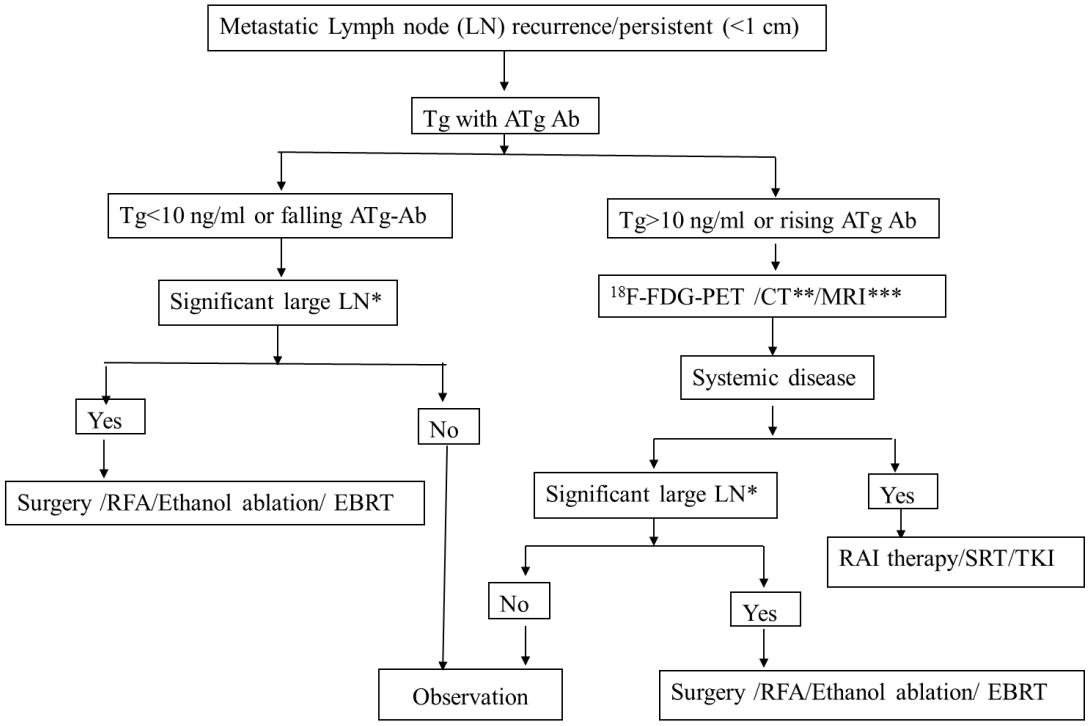
The 18F-FDG PET scan appears to be a significant investigation tool in the follow-up of patients with raised serum TG and negative whole body RAI scan or aggressive histologies [19].If value of Tg is <10 ng/ml FDG-PET should not be performed due to low sensitivity (10%-30%) and high risk of false-positive results, however in an aggressive variant of DTC and increasing titer of anti-Tg Ab, cutoff may be lowered[20]. Tg values >100 ng/ml18F-FDG PET should be done and TSH stimulation is not necessary. Tg values 10-100 ng/ml, FDG-PET should be performed after adequate TSH stimulation (TSH > 20 U/L) for optimal response [20].18F-FDG PET should also read in conjunction with standard uptake value (SUVmax), higher the SUVmax more metabolically active the lesion.

Management of Lymph Node Recurrence:

Optimal treatment for the management of recurrent lymph nodes in DTC is still debatable, especially for low volume disease. Modalities available for treatment are either surgery, RAI or observation. Local ablative therapies like alcohol ablation, radiofrequency ablation are also in use by various groups. Contentious issue is recurrences less than one centimetre. After extensive search of literature we could not find any randomized controlled trials

on this subject. Studies on subcentimetric lymph nodes are very few. Robenshtok et al[21] followed up 166 patients with low-risk thyroid cancer with an abnormal lateral compartment node with an average follow up of 3.5-year. 22% of these patients underwent biopsy prior to the decision to observe. They reported progression by 3 mm or more in 20%, by 5 mm or more in 9% and 14% spontaneously resolved without any treatment. One major limitation of their study is 78% of the patients not undergoing a biopsy, the exact number of patients who had lymph node metastases difficult to interpret. Similarly Rondeu G et al.[22] followed up 191 patients with at least one thyroid bed (TB) nodule (≤ 11 mm) on the first postoperative US performed with median clinical follow-up of 5 years. Only 9% (17/191) of patients had increase in size of at least one TB nodule. The rate of growth was 1.3 mm/year in those nodules showing an increase in size. According to ATA guidelines surgical resection ideally should be considered in case significant (shortest diameter in central neck compartment ≥8 mm and lateral ≥10mm) large lymph node or increasing in size of more than 3-5 mm in any dimension [16]. Ito et al.[23] have evaluated the impact of recurrence on prognosis and they concluded that aggressive histology, the size of the primary lesion and of the lymph node metastasis, and age at recurrence independently affected the prognosis of patients showing initial recurrence to the lymph node. Hence sub-centimetric lymph node recurrence may not impact overall survival but further studies are needed to confirm it. Osman al saif et al.[24] have reported a positive outcome on biochemical complete response (BCR) after lymphadenectomy in patients with recurrent metastatic lymph nodes. Surgical resection of persistent PTC in cervical lymph nodes achieved BCR in 27% of patients and in patients who do not achieve BCR, Tg levels were significantly reduced. This study makes a strong point in favour of surgery. Surgeon should always keep in mind the difficulty of finding sub-centimetric lymph and challenges due to scarring and fibrosis. Also there is high risk of RLN injury and parathyroid injury [25,26]. Incidence of transient vocal cord paralysis is reported to be around 0%–15% and permanent paralysis in 0%–6% . The incidence of permanent hypocalcemia is also high ranging between 0% and 10%, and of transient hypocalcemia between 10% and 60% [25,26]. All these facts should be kept in mind while planning reoperative surgery. A recurrence in CC/LC in a case where the same region was dissected is not the same as recurrence in an undissected space. Lamartina et al. [27] reported suspicious lesions located in neck areas not previously dissected in 66 patients (41%), in previously dissected areas in 70 (43%) patients, and in both dissected and not previously dissected areas in 25 patients (16%) in a series of 161 patients. Surgery in undissected space is comparatively easier and may be a better alternative to watchful observation as the cost of observation is significantly higher in addition to patient anxiety.

Flow chart below depicts the management strategy.



CASE SERIES

Case series on Cystic Adrenal Lesions: A single Institution experience

Enny Loreno[1], Ramakant Pooja[1], Garg Surabhi[1], Singh Kulranjan[1], Mishra K Anand[1], Rana Chanchal[2]
Department(s) and institution(s):
[1] Department of Endocrine surgery, King George's Medical University, Lucknow
[2] Department of Pathology, King George's Medical University, Lucknow

Corresponding Author: Pooja Ramakant, Additional Professor, Department of Endocrine Surgery, King George's Medical College, Lucknow, Uttar Pradesh. Mobile no-9791507780 poojaramakant@rediffmail.com

Abstract:

Adrenal cysts are rare and uncommon disease with only around 600 cases reported so far. They are usually asymptomatic or may rarely present with abdominal pain or fullness. Different types of adrenal cyst have been described. They are usually benign in nature. Optimum management of adrenal cysts still remain controversy, owing to its low incidence. We report four cases with different histological types of adrenal cysts, their manifestations and management.

Keywords: Adrenalectomy, adrenal cyst, retroperitoneal, laparoscopic

Introduction:

Adrenal cysts are rare and uncommon, with a reported incidence of 0.064% to 0.18%in autopsy studies [1]They account for 4-22% of all adrenal incidentaloma [2-4]Although more common in 3rd-6th decades, they can present in any age, with a female preponderance.[5] Only few case reports and case series has been published so far. Owing to its rarity, there is no specific guideline on the management of adrenal cyst so far. Herein, we report 4 patients of adrenal cysts, one each of pseudocyst, true cyst and endothelial cyst and rare case of adrenocortical carcinoma arising from a pseudocyst.

Patient 1:

A 35-year-old lady who was under investigation for hepatic cystic lesion was referred to our department for further evaluation. She had initially presented with complaints of pain in right upper abdomen for five months which was insidious in onset, dull aching, non-radiating and was relieved only on medication. There was no abdominal distension, vomiting, altered bowel or bladder habits. She had no history suggestive of a functional adrenal mass. The patient had no co-morbidities or significant past history. Her general and abdominal examination were essentially normal. Biochemical investigations showed a normal liver, renal and adrenal functioning. ELISA for Echinococcus was negative.

Ultrasonography of the abdomen, which was performed before the referral revealed an irregular cystic shadow, measuring 35x33mm in the posterior segment of right lobe of liver with foci of calcification, suggestive of right hepatic hydatid cyst. [Fig 1a]

CECT of the abdomen revealed a multiloculated cystic lesion measuring 31x32x36mm with multiple wall and septal calcification in right adrenal region. Right adrenal gland was not visualised separately from the lesion. The image was suggestive of an adrenal cystic lesion. [Fig 1b]

In view of patient's symptoms, surgical management was planned and retroperitoneoscopic adrenalectomy was performed. Intraoperatively, the lesion appeared multiloculated containing straw coloured fluid. It measured 4x3 cm in size, with all borders free. [Fig 1c] Both intraoperative and post-operative periods were uneventful and the patient was discharged on post-operative day 2. The post-operative histopathology showed a cystic lesion with fibro collagenous wall and no evident lining. Remnant of adrenal tissue is seen at the outer aspect. Histology was consistent with Adrenal Pseudocyst. [Fig 1d]

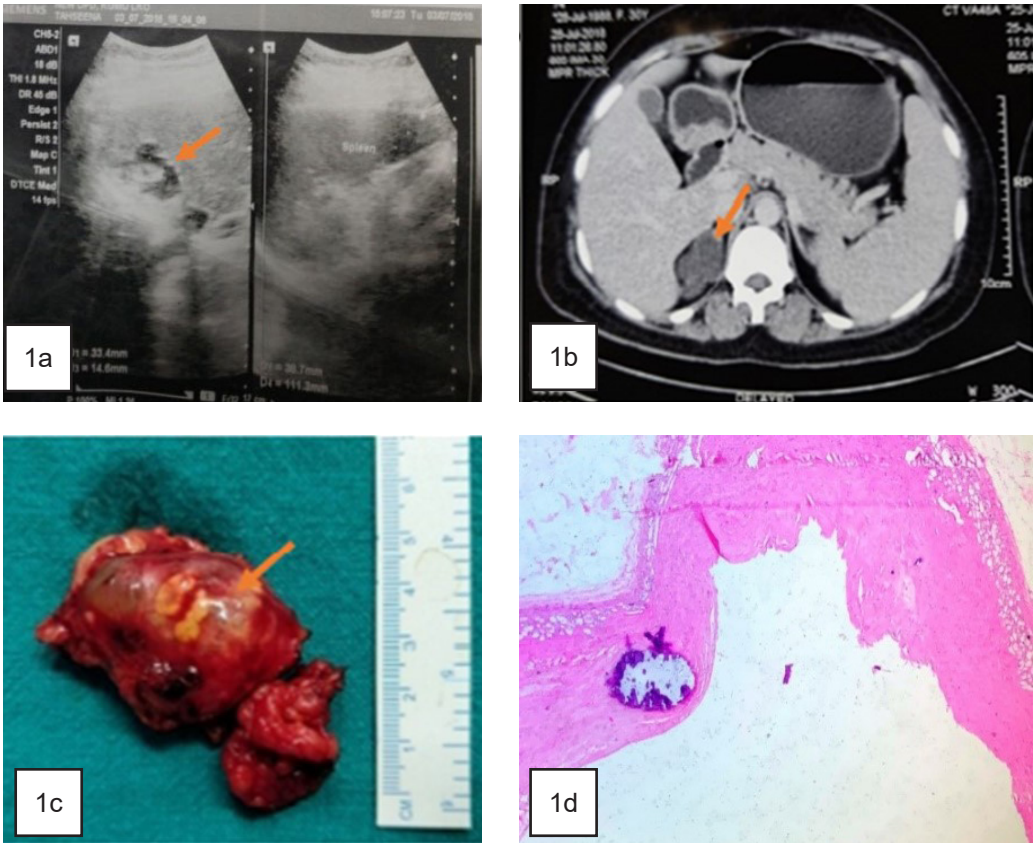


Figure 1: Adrenal pseudo cyst. a) CECT showing a multiloculated cystic lesion measuring 31x32x36 mm with multiple wall and septal calcification in right adrenal region (arrow); b) Resected specimen showing multi loculated lesion filled with fluid and; c) Histopathology shows fibro collagenous cyst wall with focal calcification and no lining. Remnant of adrenal tissue is seen at the outer aspect (Hematoxylin and eosin; 400 X).

Patient 2:

A 29 years old lady presented with complaints of dull aching pain in right hypochondriun, radiating to back. She had similar episode 7 and 3 years back for which she underwent two times guided aspiration of right suprarenal cyst. She also had history of image guided pigtail insertion for the same done elsewhere, 3 months back which was removed after 8 days. She had no history suggestive of a functional adrenal mass. Her general and per abdominal examination were essentially normal. Biochemical investigations showed a normal liver, renal and adrenal functioning.

USG abdomen revealed a mixed echogenic mass in right suprarenal region containing thick fluid (vol-449cc). [Fig 2a]

CECT abdomen revealed a well-defined rounded hypodense lesion in region of the right adrenal gland measuring approx. 79x75x78 mm with slight hyperdense echogenic area and presence of tiny specks of calcification in peripheral part with no fat component or enhancing nodule. [Fig 2b]

In view of patient history of multiple aspiration and guided drain insertion, she was managed with open adrenalectomy via trans-peritoneal anterior approach. Intra-operatively there was 8x7 cm solid cystic mass containing haemorrhagic fluid. [Fig 2c] Her histopathology revealed fibrocollagenous cyst wall lined by flattened endothelial cells along with remnants of adrenocortical tissue consistent with endothelial cyst. [Fig 2d]

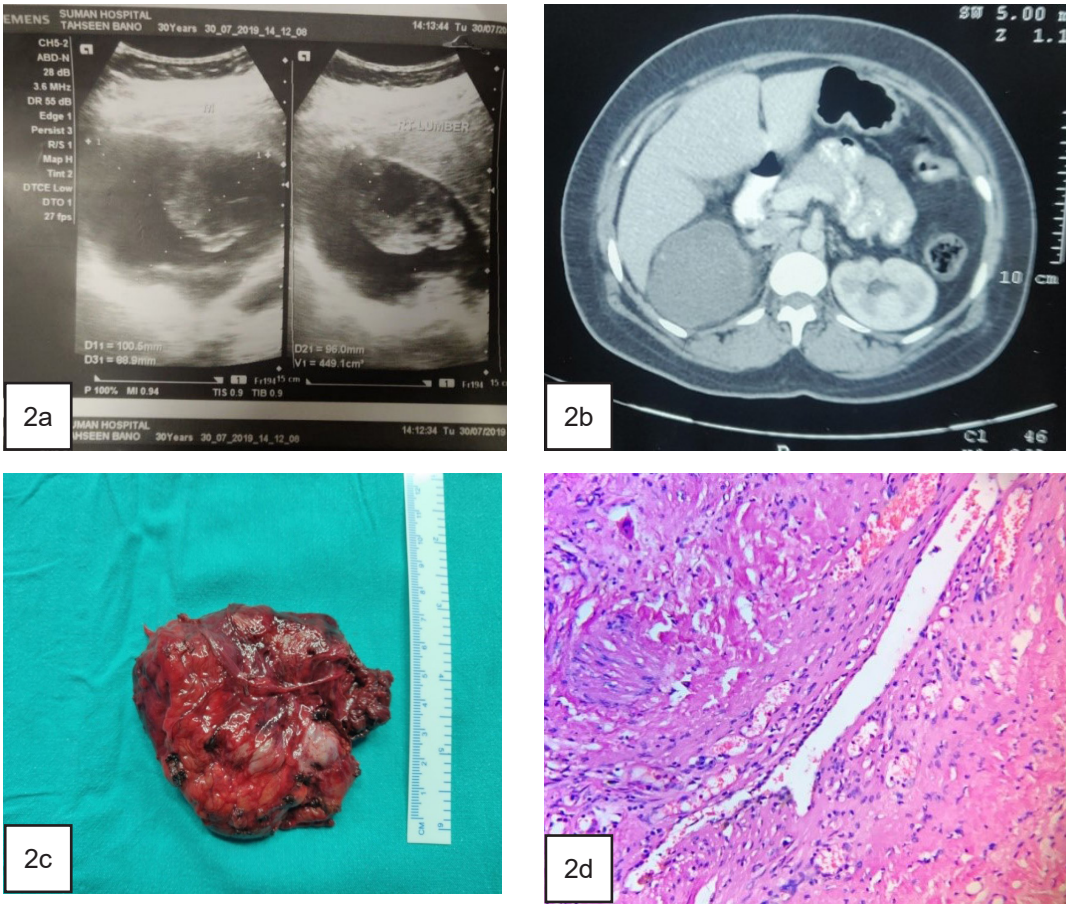


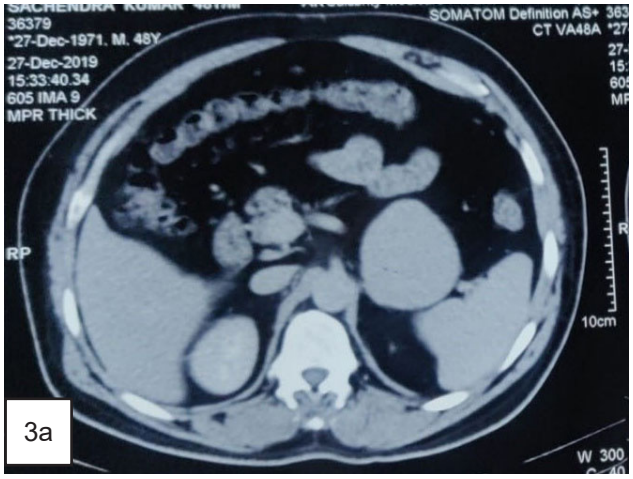
Figure 2: Adrenal Endothelial cyst. a) USG abdomen showing a mixed echogenic mass in right suprarenal region (arrow); b) CECT abdomen showed well defined right adrenal cyst as round hypo dense lesion measuring approx. 79x75x78 mm with internal haemorrhage as slight hyper dense echogenic area in it (arrow); c) Resected specimen showing right suprarenal mass measuring 8 x 7 cm with cystic and solid component and; d) Histopathological evaluation display cystic structure with fibrocollagenous wall lined by flattened endothelial cells and red blood cells in the lumen (Hematoxylin and eosin; 400 X).

Patient 3:

A 48-years aged gentleman who was under evaluation for abdominal fullness and dyspepsia from Medical Gastroenterology was diagnosed to have left adrenal lesion for which he was referred to our department for further evaluation. He had no history suggestive of a functional adrenal mass. The patient had no co-morbidities or significant past history. His general examination and abdominal examination were essentially normal. Biochemical parameters including hemogram, liver, renal and adrenal function were within normal limits.

CECT abdomen showed well-defined mildly hyperdense thin walled non enhancing lesion with HU 95 measuring 6.3x6.4x6.6 cm in the retroperitoneum closely abutting pancreas and left adrenal with subtle calcification at inferior aspect of lesion? Adrenal cyst. [Fig 3a]

Although the patient had no significant symptoms, since the size of the lesion was > 6cm, surgery was planned and he was managed by laparoscopic adrenalectomy via anterior approach. Intraoperatively, there was a well circumscribed cystic mass lesion measuring 6 x 5 cm. His final HPE was consistent with true adrenal cyst. [Fig 3b]



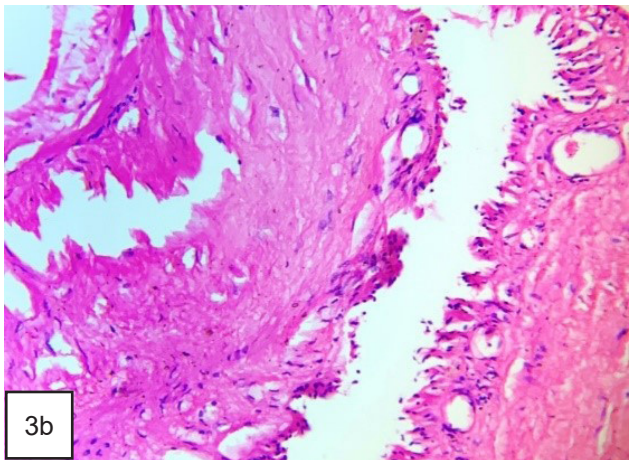


Figure 3: Epithelial adrenal cyst. a) USG abdomen showing (arrow) a well-defined hypo-echoic lesion in left suprarenal region measuring 64x52 mm (? adrenal origin); b) CECT showing a well define, round to oval, hypo dense lesion with hyper dense thin wall measuring 6.3 x 6.4 x 6.6 cm in the retro peritoneum closely abutting pancreas (arrow); c) Cyst wall lined by single layer of columnar epithelial cells (Hematoxylin and eosin; 400 X).

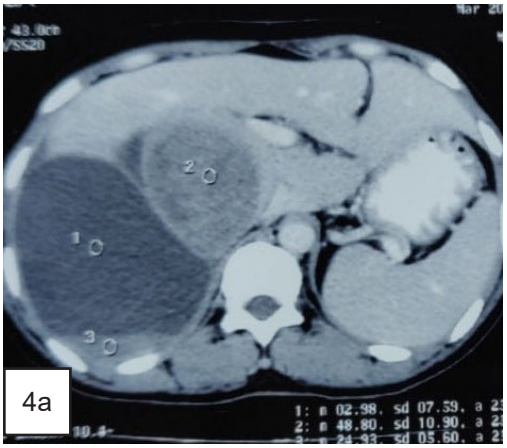
Patient 4:

A 40 years aged lady, presented with pain in right hypochondrium and lumbar region for 1 year which was associated with generalised weakness, fatigue and constipation for the past one month. No history suggestive of a functional adrenal mass. On per-abdominal examination, a lump of size 13x10 cm was palpable in right hypochondrium extending to lumbar region, crossing the midline which was firm to hard in consistency with smooth surface. Serum and urinary catecholamines were unremarkable. During investigation, a well-defined para-renal 13×10 cm septated cyst was identified on CT. The right adrenal gland was not separately identified from the mass, suggesting adrenal origin. [Fig4a]

In view of large size and malignant potential of complex cysts, right open adrenalectomy was performed via anterior transperitoneal approach. Per-operatively, there was a very large predominantly cystic mass measuring 15x15cms with solid areas which was densely adhered to inferior surface of liver.

Histopathological evaluation revealed a cystic lesion with fibrocollegenous cyst wall and absence of any lining. These were a solid component composed of sheets of atypical cells with resemblance of cortical cells. [Fig 4b] Mitosis was >5/10 high power field. Areas of necrosis and haemorrhage were also seen along with presence of atypical mitotic figures. The modified Weiss score was 4 suggesting

adrenocrtical malignancy. These tumour cells were immunohistochemically positive for synaptophysin, vimentin, melan A and inhibin with no expression of chromogranin and CK7, CK20. Ki67 proliferation index was 5%. Hence, the case was finally diagnosed as Adrenocortical carcinoma arising from a pseudocyst with poor prognostic markers. The patient is lost to follow up.



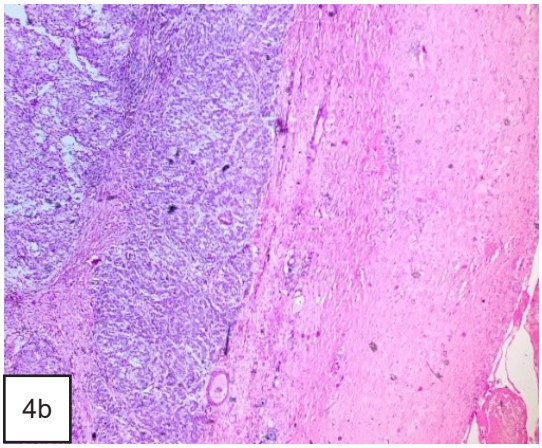


Figure 4a: Cystic adrenocortical carcinoma. a) CT scan shows well-defined para-renal 13×10 cms septated cyst (arrow) compressing the adjacent bowel and right lobe of liver. The right adrenal gland was not separately identified from the mass, suggesting adrenal origin and b) Microscopy shows fibrocollagenous cyst wall with sheets of atypical epithelial cells having high nucleo-cytoplasmic ratio, pleomorphic nuclei and moderate amount of eosinophilic cytoplasm (Hematoxylin and eosin; 400 X).

Discussion

Adrenal cyst was first described by Viennese Anatomist Greiselius in 1670 in a 45 year old man who died due to rupture of an adrenal cyst weighing more than 4 kg.[6] The reported female to male ratio in literature is 3:1. [5] They are usually unilateral and bilateral cysts are seen in only about 8-15 % of cases .[1] Most of these cysts are benign in nature with reported incidence of malignancy in only 7 % of cases.[7]About 95% of these malignant lesions are metastases from other primary epithelial tumours(lung, kidney, colon, breast, pancreas, liver and stomach), 3% are pheochromocytoma and remaining 2% adrenocortical carcinomas.[3, 8] They are usually asymptomatic and are discovered incidentally. However, in about 39% of cases, they may present with large mass lesions and pain due to haemorrhage or cyst rupture. Rarely (9% of cases) adrenal cysts are associated with hypertension, probably due to compression of adrenal artery or renal medulla [3]. In our series, three of them had different modes of presentation. Our first patient had small but symptomatic adrenal mass, second patient presented with history of multiple aspirations and the third patient presented with large adrenal mass with complaints of only vague abdominal fullness.

The first classification of adrenal cyst was given by Terrier and Lecene in 1906. They classified adrenal cyst into haemorrhagic, endothelial, congenital retention, cystic adenomas and parasitic types.[9] Following which many other classifications were formulated eventually. However, the most accepted classification till date was given by Foster in 1996. He classified adrenal cyst into four types based on histological types on autopsy and incidence: Endothelial cyst (45%), pseudocyst (39%), epithelial cyst (9%), and parasitic cyst (7%).[6]

Pseudocysts are most common among all adrenal cysts across different studies with an incidence of 39%. [6] They are usually large and uniloculated with walls devoid of any cellular lining.They vary greatly in size, ranging from few millimetres to more than 50cm.[11] Association of pseudocyst with adrenal neoplasm has been reported in about 18.7-44% of cases.[12] Among the malignancies found in adrenal pseudo cysts; adreno-cortical carcinoma (ACC) is by far the most common [13].

Endothelial cyst are also known as simple cysts. They are the most common among adrenal cysts in autopsy series with incidence of 45%, but account for only 2-24% of clinically symptomatic lesions. They are usually small in size; with an average size of less than 2cm.The walls of these cysts are lined by

smooth flattened endothelial lining [7]. Two subtypes of endothelial cyst are described; lymphangiomatous type (94%) and angiomatous type [6%].[5, 7]Epithelial cyst are true cysts. They are mesothelial in origin and their walls are lined by smooth flattened epithelial lining [12]. Different subtypes of epithelial cysts are reported, namely glandular or retention cyst, cystic adenomas, and embryonal cyst.[12] Parasitic cyst are rare with an incidence of 7 % [6]. Echinococcosis is the most common causative organism. They have thick walls with or without calcification.

Till date there have been only around 600 cases of adrenal cyst reported so far. The largest case series to date was reported by Erickson LA et al, in 2004, where he reviewed 41 cases of adrenal cyst (32 pseudocyst, 8 endothelial cyst and 1 epithelial cyst). [10]

Imaging modalities for adrenal cyst include ultrasound abdomen, which has a reported sensitivity of 60-70% for detecting adrenal cyst.[11] Adrenal cyst on ultrasound reveal well-defined, round to oval anechoic structure showing posterior acoustic enhancement. Hyperechoic pattern may also be seen on ultrasound in case of haemorrhage in the cyst. Contrast enhanced computed tomography [CECT] of the abdomen is the gold standard imaging modality with a sensitivity of 85-100% and specificity of 95-100% [11]. On CECT, true cysts characteristically have fluid attenuation, usually less than 20 HU, have smooth borders with thin non-enhancing walls. Lack of contrast enhancement on CT favours the diagnosis of adrenal cyst. Calcification can be noted in around 15-70% of cases which can be either rim or nodular calcification. MRI has a sensitivity of 100 %.[15] On MRI, simple cyst appear hypo intense on T1 weighted images and hyper intense on T2 weighted images without any soft tissue component or internal enhancement. In case of haemorrhage in adrenal pseudocysts, they appear hyper intense on both T1 and T2 weighted MRI images.

Optimum management of adrenal cysts still remain a controversy, owing to its low incidence. Surgical management, whether open or minimally invasive depends on a surgeon's preference, adrenal lesion size and characteristics on imaging. Surgery is usually indicated in functional cysts, malignant or potentially malignant cysts, symptomatic cysts of any size, asymptomatic cysts of size more than 5cm and those patients with uncertain follow up.[7,16]

In our first patient, surgical removal was done in spite of lesion being <4 cm in greatest dimension, due to presence of chronic pain. The remaining cases also underwent adrenalectomy because of larger size as well as presence of symptoms. For lesions measuring more than 6 cm, open adrenalectomy was found to be a better operative approach, as these lesions were found to have dense adhesions with adjacent structures (seen in 3 out of 4 patients). The reason for this is not clear, but it may be due to cystic fluid permeating through the capsule causing adhesions with adjacent tissues. We also experienced this adhesive plane making difficult dissection in our patient series.

Chien et al, in 2008 reviewed the importance of surgical management in patients with adrenal cyst wherein he reported 25 cases of adrenal cyst (16 pseudocyst, 8 endothelial and 1 epithelial cyst) where seven adrenal pseudocyst were associated with tumour including two pheochromocytomas, one neuroblastoma, one adrenal cortical carcinoma, one adrenal cortical adenoma, one myelolipoma, and one schwannoma. He concluded that because of their heterogeneous aetiology and overlapping clinical findings, definite diagnosis relies on extensive sampling and thorough microscopic examination in order to exclude the possibility for coexisting tumour.[12]

Conservative management is apt in those with uncomplicated/asymptomatic cysts <5cm.[12]A minimum of 18 months of follow up with repeat CT every 6 months is indicated. Aspiration of cyst can be considered as an alternative to surgery in case of surgically unfit patients.[1, 5, and 7] Marsupialisation or decortication have also been tried as alternatives to surgery for large cyst specially those cyst which are adherent to multiple organs where excision may be difficult[5]. Sclerotherapy using absolute alcohol has also been described but it is associated with high recurrence of 30-50 % [1, 5].

In conclusion cystic adrenal lesions are rare and uncommon disease with varied manifestations and sometime present with diagnostic dilemma. Proper investigation including CT or MRI is essential for defining adrenal cystic lesion and also for differentiating it from cystic lesion of adjacent organs. Surgery is the treatment of choice in symptomatic case and histopathological examination is essential for definitive diagnosis.

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CASE REPORT

Intra-operative Parathyroid localization in Primary Hyperparathyroidism in a resource constrained part of India- a case report and a review of literature

Dr. Sudhi Agarwal MS, MCh, F MAS, D MAS
Consultant and Head, Department of Breast, and Endocrine Surgery.
Nutema Hospital. Meerut
Email –sud_soni@rediffmail.com

Background

In the Indian subcontinent, the concept of endocrine surgery is gaining its popularity. Every year highly qualified endocrine surgeons are passing out from their reputed institutes. Many of them operate parathyroid tumors in primary hyperparathyroidism (PHPT) in the areas with limited facilities like the intra-operative nuclear scanning and intra-op PTH estimation. Should the surgeons stop practicing parathyroid surgery in the absence of such high-end investigations or they can make use of some commonly available adjuncts like methylene blue to localize the abnormal parathyroid glands intra-operatively especially in complicated cases? The role of methylene blue in various localization studies like sentinel lymph nodes biopsies are well established, but its role in the parathyroid localization is still debatable. With the help of a case report, we reviewed the literature to find out the safety and efficacy of the methylene blue in the intra-operative localization of abnormal parathyroid glands and whether it can substitute the not so readily available expensive investigations.

Case Report

A 44 years old male, sub-inspector by occupation presented with the complaints of recurrent nephrolithiasis, frequent graveluria, and recurrent urinary infections for 18 years. Other than that he did not exhibit any features of overt metabolic bone disease, syndromic features, gatro-intestinal symptoms, or body weakness. He had a non-contributory family history, but had compromised renal functions on Renal Dynamic Scan and underwent repeated nephrolithotomies both open and endoscopic for renal stones. He was under work up in the reputed institute of the country, where he was diagnosed as a case of Primary Hyperparathyroidism biochemically, but the lesion was not localized even with repeated attempts of ultrasound, MIBI scan, and CECT Neck. Since he only had the reports and not the images, we repeated the investigations which further confirmed the diagnosis of primary hyperparathyroidism with metabolic bone disease and nephrocalcinosis. Table 1. In the MIBI scan, though, the endocrine surgeon could appreciate the subtle lesion in delayed images in the right inferior region; the nuclear medicine physicist reported it as negative for any abnormal uptake. Keeping in mind the importance of imaging, the endocrine surgeon and the experienced radiologist together did the USG neck and subsequent CECT neck and could appreciate the subtle lesion in the right inferior region, but the lesion was too small to be sure of parathyroid tumor. (Figure 1.).

Owing to the inconclusive pre-operative localization studies, he was planned for bilateral neck exploration under general anesthesia. Though we had the facility of parathyroid scans we lacked facilities of intra-op nuclear scanning, intra-operative frozen section biopsies or intra-operative parathyroid measurement. After proper consent, we took the patient for bilateral neck exploration with intra-operative methylene blue infusion technique to aid our detection of abnormal parathyroid.

Since the team was new to this procedure, to avoid the risk of any mishap, after a test dose, we infused the methylene blue solution @ 2mg/ kg body weight in 100 ml of normal saline, (despite the recommended 5-7.5 mg/kg of body weight), started 20 to 30 minutes before induction and completing

just before the incision. During exploration, we found a clear bluish discoloration of the right inferior parathyroid gland. The gland was enlarged 1x 0.5 cm, elongated, and encapsulated. All the other three glands were identified and were seemingly normal and unstained. The thyroid was also slightly bluish in colour. The right inferior parathyroid gland was excised and biopsies were taken from the other three parathyroid glands (Figure 2). Since our institute did not have the facility for frozen section, we sent the tissue to definitive histopathological examination only. Postoperatively, the patient developed mild hypocalcaemia which was managed with oral calcium and vitamin supplements. The histopathology reported as parathyroid adenoma with normal other three parathyroids. Before his transfer to another city, he came for follow ups for next 2 years during which time his nephrocalcinosis decreased, with no new stone formation. His frequency of urinary infection and fever decreased with improvement in renal functions. His iPTH dropped to 26 pg/ml (14-72 pg/ml) with serum calcium 8.9 mg/dl (8.5-10.5 mg/dl).

Table 1:- Important pre-operative investigations of the patient

iPTH	235.8 pg/ml	15- 65
S Calcium	11.2 mg/dl	8-10
I Phosphorous	2.6 mg/dl	2..5- 4.5
25 OH vitamin D	13.2 ng/ ml	20-100
Uric acid	8.4 mg/dl	2-7.4
Alkaline phosphate	479 mg/dl	80-240
TSH	4.51	0.3-4.2
Prolactin	8.32 ng/ml	6- 29.9
BMD	T SCORE	Z SCORE
WRIST	-2.9	-2.6
HIP	-1.6	-1.1
SPINE	-1.9	-1.8

Discussion

The awareness regarding the parathyroid surgery is on the rise. The trained endocrine surgeons are passing out every year from their reputed institutes to work at new and remote places creating awareness about these disorders and providing surgical facilities to the needy patients. The endocrine surgery being at its initial phases in those regions, many times the high-end investigations are not available (1, 2, 3, 4, 5, 6). Many surgeons with an interest in parathyroid surgery are thus stuck to decide whether or not to operate a patient with inconclusive parathyroid localization. But with an optimistic vision, if we look back at the history of parathyroid surgery, there was a time when "an experienced parathyroid surgeon" was considered the "best to localize the parathyroid tumors". In this case, we tried to prove this dictum with the help of a commonly available and cheap dye known as methylene blue.

About methylene blue

Methylene blue, also known as methylthoninium chloride, was first developed by Heinrich Cairo in 1876 (7). It is the first fully synthetic drug used in medicine (8, 9). Since its first use in medicine as a treatment for malaria in 19th century, it has been used in a variety of clinical conditions like methemoglobinemia (10), plaque psoriasis (11)urinary tract infection (12), cyanide poisoning (13), ifosfamide poisoning (14), septic shock and anaphylaxis (15) and as a dye in cancer surgeries (16), sentinel lymph nodes biopsies (17), sinus and fistula surgeries (18) and to monitor the compliance with the psychiatric medicines. (19).

Its dry form exists as dark green crystal and in solution, it turns into the deep blue. It can be given both orally and intravenously and for external use also. It is excreted by kidney, liver which results in the bluish discoloration of the urine and stools for several days after administration. Doses over 7.5 mg/kg may result in gastrointestinal symptoms. It shares the structural similarity with monoamine oxidase inhibitors and therefore may precipitate the signs and symptoms of serotonin-induced neurotoxicity with drugs that increase the levels of central serotonin levels like the SSRIs. (20)

Methylene blue in parathyroid surgery

In 1971, Dudley first advocated the use of methylene blue infusion in parathyroid surgery In his study of 17 patients, he found 41 abnormal glands and had a 100 percent cure rate. He used a calculated dose of 5 mg/kg body weight in 500 ml of 5% dextrose and 1/5 normal saline and given intravenously for one hour before surgery. In his experience, the color of the abnormal parathyroids was stained dark blue to purple whereas the normal parathyroids, thyroids, and muscles stained dusky slate blue. The intensity of staining increases up to one hour after infusion lasts for 20 minutes before diminishing over the next 2-3 hours. (21)

DJ Sherlock et al, in his study on 40 patients with hyperparathyroidism found almost 100% detection rate of pathological glands which are characteristically more intensely stained than the normal parathyroid

glands. The staining was consistent. The glands were visualized through various tissue layers, which aided in surgical dissection. (22)

MH Thabet et al. published his results of intra-operative use of methylene blue infusion @ 7.5 mg/kg, as an adjunct to Minimally Invasive, Endoscopic Assisted Parathyroidecomy (MIEAP). In his study on 9 patients, the adenoma detection rate was 100% with no staining of normal parathyroid glands with the additional advantage of decreased surgical time (23)

MS Shamim, in his study, tried to score the uptake of the methylene blue by the parathyroid glands. Score 0- no uptake or no or very little difference in color, no blue tinge; Score 1- Little uptake, a mild difference in color, very light blue tinge, only obvious on close observation; Score 2 – good uptake, the moderate difference in color, blue tinge, visible without difficulty; Score 3 –Excellent uptake, gland turned deep blue to purple color. 8 glands were removed from the 5 patients, one of them had MEN syndrome. Four out of eight glands showed excellent uptake, three showed good uptake and one showed no uptake (Patient with MEN syndrome). (24)

Bewick J in his study found a sensitivity of 78.9% with methylene blue which was in line with the USG (79%) and parathyroid scintigraphy (88%). The study recommended methylene blue as an adjunct to these measures by complementing and confirming the finding especially in multiglandular and ectopic diseases where the sensitivity rates are quite lower. It helps in distinguishing the blue stained parathyroid gland from the other tissues like lymph nodes. (20)

None of the studies faced any problem associated with the administration of the dye. The patient's acceptability was excellent except. The side-effects are usually mild and self-limiting, like bluish discoloration of urine and other body fluids, which is very well tolerated if the patient is counseled pre-operatively. It demonstrates the synergistic effects of anesthetic drugs and can prolong the arousal time; therefore, they must be used judiciously. Overdosage of anesthetic drugs may lead to methylene blue encephalopathy; therefore, patients with delayed arousal must have brain monitoring. Though neurotoxicity is a dreaded complication, it is very rare and almost all these neurotoxicity are reported in patients receiving anti-depressants especially SSRI (Selective Serotonin Re-uptake Inhibitors). This can be avoided either by not giving methylene blue to those taking SSRI or switching the patient to other safe alternatives in consultation with the physician.

Haciyanli M et al, reviewed their results of the ultrasound guided methylene blue injection in the parathyroid tumors of the patients with re-operative recurrent hyper-parathyroidism. In their technique, they injected a 0.2 ml of the 1:5 diluted 1% methylene blue directly into the adenoma with a tuberculin syring and before removing the syring they instilled another 0.1 ml of the dye just under the skin to guide the incision. In their experience the blue dye was not scattered around and confused the anatomy (25). Though they reported this technique as useful,but pre-operative localization by means of staining the parathyroid glands can only be useful if the surgeon is sure of the particular lesion as parathyroid tumor only.

A very detailed review published by Patel et al showed methylene blue to be efficacious with a 100% staining rate of abnormal parathyroid glands. The methylene blue arm group had a 100% cure rate compared to the non-methylene blue arm. The untoward effects were high in the methylene blue group but the majorities were harmless like discoloration of urine and the serious side –effects were limited to those taking SSRIs. (26)

Table 2: - Summary of the methylene blue staining characteristics in parathyroid surgery.

S	Study type/ sample size	Dose	Timing of infusion	Staining of abnormal glands	FP/ FN	Differentiating features (if any)	Cure rates	Adverse drug reactions/ Complications
Bewick J (20)	Prospective/ 98cases	3.5 mg/kg BW in 500 ml of DNS	One hour prior to surgery	78.6%	FN - 15.5%; FP- X	X	X	Neurotoxicity- 0 Hypotension- 2 Wheezing – 1 Transient bradycardia- 1 Injection site pain – 2
Dudley (21)	Prospective/ 17 cases	5 mg/kg BW in 500 ml DNS	One hour prior to surgery	41 out of 68 parathyroid glands found Abnormal glands- dark blue to purple	X	Normal glands- dusky slate blue;Thyroid glands, thyroid cysts and strap muscles took light blue tinge	X	No troublesome side-effects
DJ Sherlock et al (22)	Prospective/ 40 cases 12 with secondary or teriary HPT	5-7.5 mg/kg BW	One- two hours prior to surgery	All 4 glands were demonstrated in 38 patients. In 2 cases 3 glands were demostrated	X	Normal glands stained less deep than pathological glands. Adenomatas stain dark blue and hyperplastic stained light blue	39 out of 40 patients achieve eucalcemia. One patient had supernumery ectopic gland requiring re-exploration	One case of nausea due to rapid infusion
MH Thabet et al. (23)	Prospective/ 9 cases with PHPT	7.5 mg/kg BW in 500 ml 5D.	Started 20 minutes before incision	All tumors stained (100% accuracy and 100% specificity)	0%	No staining of surrounding tissues, like thyroid, lymph nodes and thymus	100%	Injection site pain due to high flow
MS Shamim (24)	Prospective/ 5 cases	20 ml of 2% methylene blue in 500 ml NS	15-30 minutes prior to induction till incision	4/8 showed excellent uptake; 3/8—good uptake; 1/8—little uptake	X	X	X	Only transient discolouration of urine
Patel et al (26)	Systematic review/ 39 studies	5-7.5 mg/kg BW in 200 to 500 ml of infusion fluid	Majority completed infusion just before incision. Few gave boluses or Infusion after intubation	Overall median staining rate SGD and MGD was 100%	Median staining of - Normal glands – 59%; Lymph nodes- occasional; Thyroid - 14.4%	X	Overall median cure rate (SGD and MGD) for methylene blue arm was 100% and non-methylene blue arm was 98%	Common- pseudocyanosis, pseudohypoxia, temporary discoloration of urine, pain at infusion site, nausea; less common – neurotoxicity, esp in patients already on SSRIs

Conclusion

During the last few decades, the role of methylene blue is taken over by newer techniques. Its worth is under-estimated and its side-effects are over-hyped. In developing countries or areas with budding endocrine surgery, it is not possible to use these varieties of investigations due to lack of availability and cost. "The eyes don't see what the mind don't know"- An experienced parathyroid surgeon is a must for the parathyroid surgery, however the preferential staining of the abnormal parathyroid tissues with methylene blue can assist the surgeon especially in technically challenging cases in a resource constraint condition to decide the extent of the parathyroid excision. The world literature also supports the use of methylene blue infusion in an effective and safe method, which can compensate for the non-availability of expensive and versatile per-operative investigations. Additionally, it has the advantages of being cheap, readily available, requiring no additional equipment and with no serious side-effects except for those taking SSRIs, which can easily be avoided by taking the drug history. Therefore the use of methylene blue in the parathyroid surgery must be re-considered to achieve the cost-effective management of the primary hyperparathyroidism

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CASE REPORT

A Challenging Case of Life-threatening Hypercalcemic Crisis- A Case Report of Rare Intrathyroidal Parathyroid Neoplasm with Uncertain Malignant Potential

Poongkodi K [1,2,3], Premkumar A[4], Lakshmi Viniya[5]

[1] Assistant Professor of Endocrine Surgery, Government Mohan Kumaramangalam Medical College, Salem; Madras Medical College, Chennai

[2]Research scholar, TN Dr.MGR Medical University, Chennai

[3] Consultant Endocrine Surgeon, SKS Hospital and Postgraduate Institute, Salem-636004

[4] Consultant Endocrinologist, SKS Hospital and Postgraduate Institute, Salem-636004

[5] Consultant Pathologist, SKS Hospital and Postgraduate Institute, Salem-636004

Hypercalcemic crisis is a potential life-threatening condition defined by serum corrected calcium > 14mg/dl(>3.5mmol/L) and signs and symptoms of acute calcium intoxication with significant deterioration of cardiac, renal, pulmonary or neurological function(1,2). It is an uncommon endocrine emergency, mostly caused by severe sporadic primary hyperparathyroidism (SPHPT) in the out-patient setting. We present here, a case of hypercalcemic crisis in a non-diabetic, non-hypertensive 44-year old man with right-sided neck mass, referred as SPHPT with progressive renal failure. Cervical ultrasound (Fig-1) revealed two well defined hypoechoic solid nodule measuring 23X31mm and 17X19 mm in the postero-inferior aspect of right lobe of thyroid with increased intralesional vascularity on Colour doppler (Fig-2). Thyroid gland was normal in size with homogenous echotexture. Ultrasound of the abdomen showed renal and pancreatic calcinosis. Laboratory investigations revealed elevated levels of serum calcium = 18.3 mg/dl, intact parathyroid hormone (iPTH)= 20176.4 mg/dl, creatinine = 3.1 mg/dl, phosphorus= 5.5 mg/dl and low sodium= 122 mmol/l, and potassium= 2.6 mmol/L. Adequate hydration, correction of electrolyte imbalances and 2 cycles of calcium free hemodialysis allowed rapid fall of calcium to 14.5 mg/dl. Owing to the non-availability of scintigraphy scans for localization, bilateral cervical exploration as quasi-emergency under general anesthesia was planned. Intra-operatively, thyroid gland was enlarged with hard mass in the right lobe of thyroid and few enlarged lymph-nodes. Parathyroid gland was searched in the eutopic sites of superior (PIV) and inferior parathyroid gland (PIII) (arising from the fourth and third pharyngeal pouch respectively), and also sites of extended embryonic migration (which is common in PIII) and could not be found except for the normally placed PIV in the left side. Therefore, we proceeded with right hemithyroidectomy with enbloc-resection of the mass, which was densely adherent to trachea medially and carotid sheath postero-laterally (Fig-3). Cut-section of the gross specimen (Fig-4) showed intra-thyroidal mass (Fig-5), which was consistent with parathyroid on frozen section. In addition, end point of the surgery was monitored by > 50% fall of iPTH (10-min post-excision sample) from pre-incision iPTH on Intra-operative PTH quick assay. However, in view of severe hypercalcemic crisis, severe PHPT and palpable neck mass with indentation on the trachea, parathyroid carcinoma was suspected and ipsilateral central compartment neck node dissection was carried out. Post-operatively, patient developed hungry bone syndrome with rapid fall of calcium and phosphorous. Repeated Iv calcium infusions were given along with oral calcium and vitamin D supplements. Additionally, Tab.Magnesium oxide 400 mg P/O for 3 days was administered for correction of resistant hypocalcemia. Calcium and renal function normalized over days. Histological examination (Fig-6 and 7) revealed Intrathyroidal parathyroid neoplasm (surrounded by thyroid tissue on all aspects) with uncertain malignant potential and reactive nodes. Parathyroid carcinoma is

notorious for difficulty in establishing its diagnosis, the absolute criteria being local invasion and distant metastases(3). Loss of parafibromin, loss of APC and high-MIB index are useful immunohistochemistry markers for distinguishing parathyroid carcinoma from adenoma, but could not be afforded. Even in histologically proven parathyroid carcinoma, a long lag time is observed between the diagnosis and appearance of metastases. Hence, long-term close follow-up surveillance with serum corrected calcium is recommended. At 5-years post-surgery, patient remains eucalcemic.

Learning points:

Hypercalcemic crisis is potentially a life-threatening endocrine emergency

It is associated with higher rates of surgical failure than non-crisis patients especially, in the setting of intrathyroidal location of abnormal parathyroid gland.

Prompt, appropriate and expeditious parathyroidectomy portends excellent prognosis

Parathyroid carcinoma is rare, accounting < 1% of SPHPT cases

Surgery is the only curative treatment for parathyroid carcinoma

En-block resection of the mass with ipsilateral thyroid lobectomy +/- central compartment neck node dissection is procedure of choice for parathyroid carcinoma.

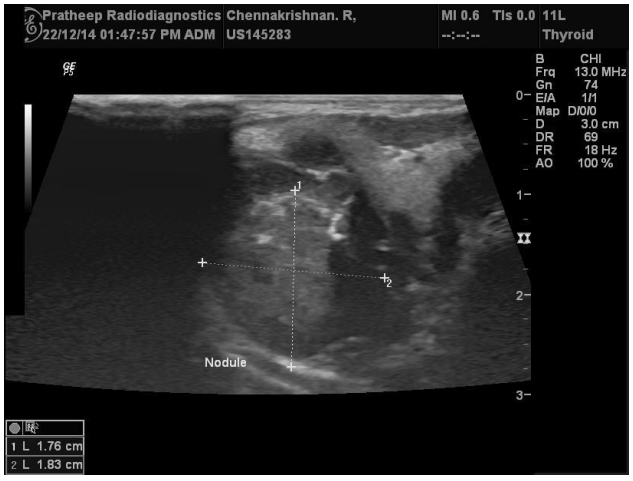

Fig-1. High frequency cervical ultrasound showing hypoechoic solid lesion in the postero-inferior aspect of right lobe of thyroid gland

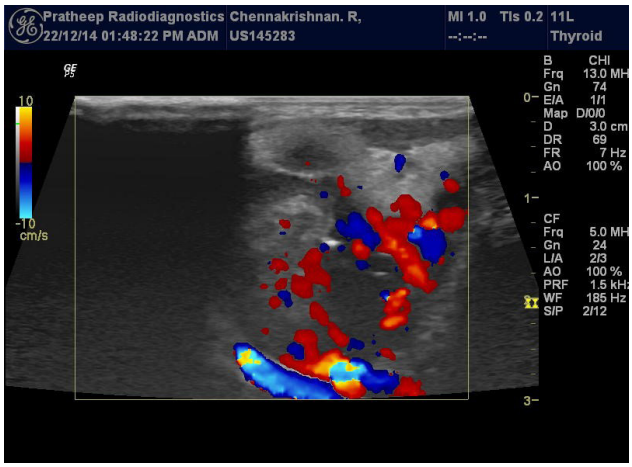

Fig-2. Colour Doppler imaging shows increased intralesional and peripheral vascularity

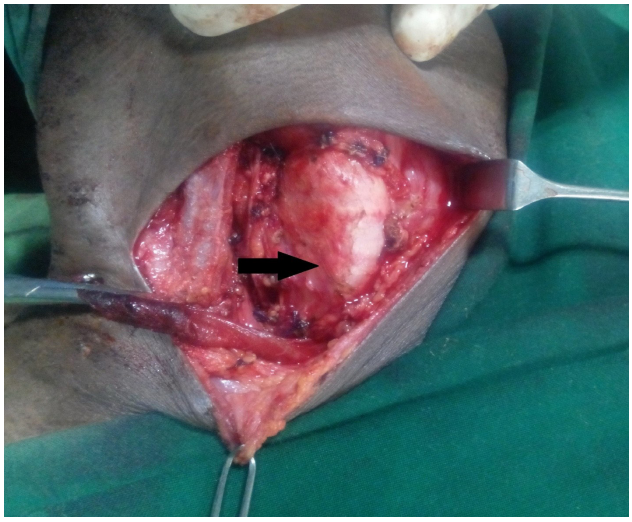

Fig-3. Arrow showing the indentation on the trachea caused by the hard mass in the right lobe of thyroid after right hemithyroidectomy.

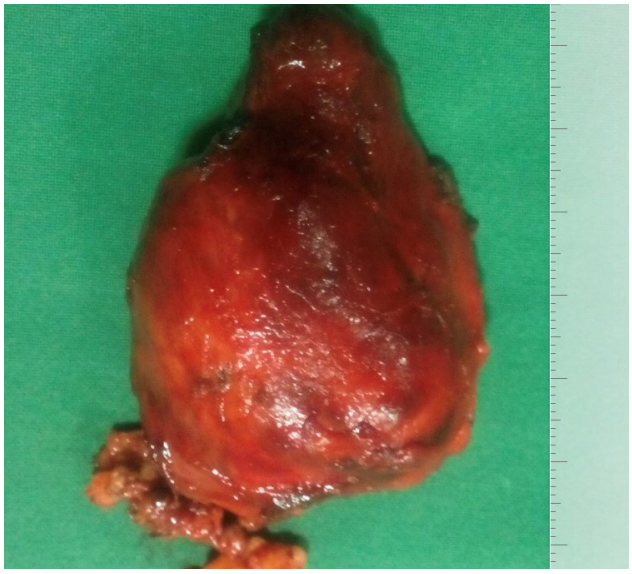

Fig-4. Gross specimen of right hemithyroidectomy and ipsilateral central compartment nodes.

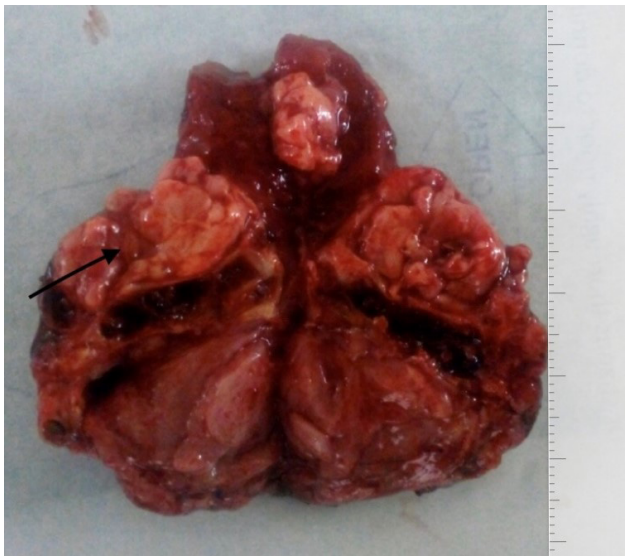

Fig-5. Cut-section of right hemithyroidectomy specimen showing intrathyroidal mass lesion.

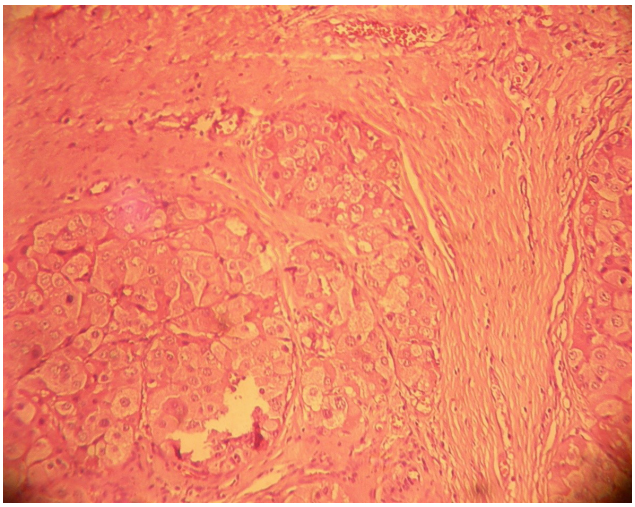

Fig-6. Microscopy 40X H&E. showing lobules intersected by broad fibrous strands

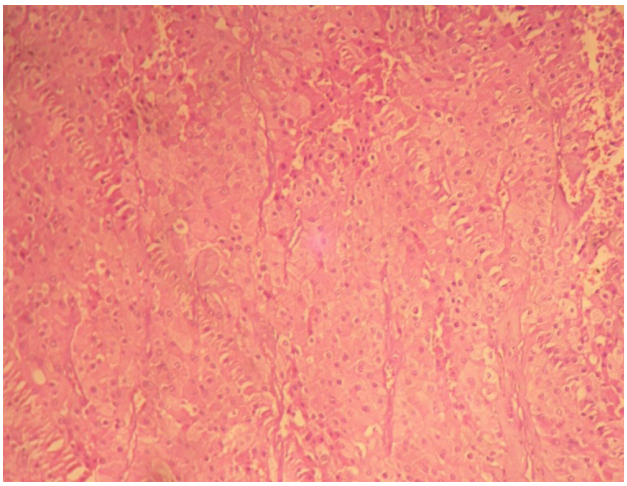

Fig-7. High power microscopy showing islands of medium sized cells with oval vesicular nuclei, nucleoli and moderate eosinophilic cytoplasm

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IMAGE OF INTEREST

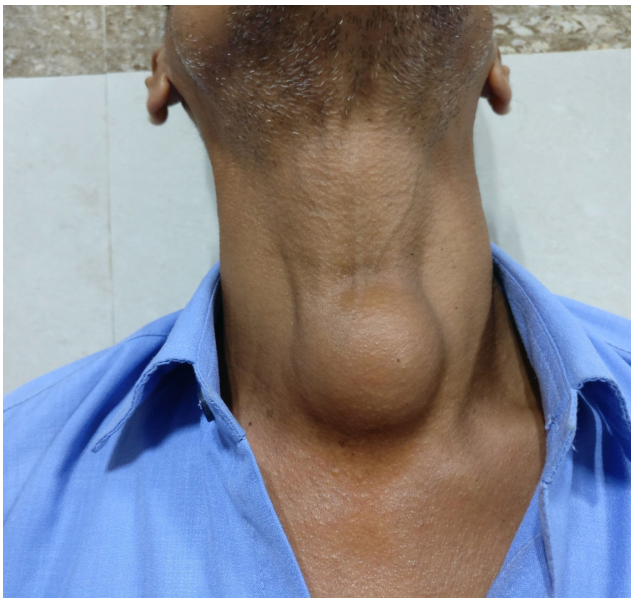
Endocrine Image- Masqueraders of thyroid swelling

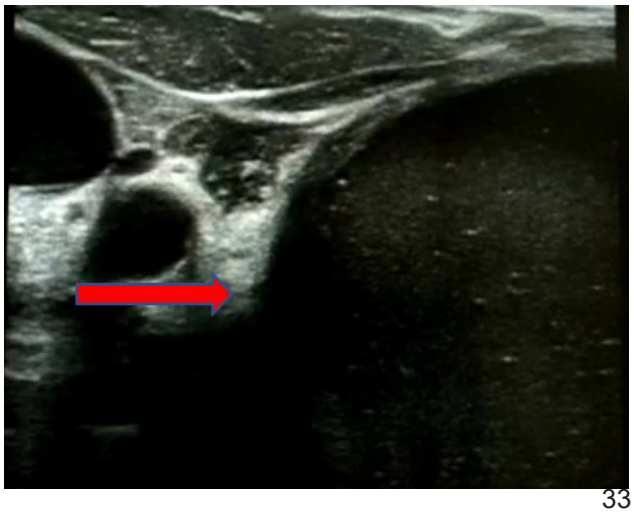
Surabhi Garg [1], Pooja Ramakant [2], Kul Ranjan Singh [3], Anand K Mishra [4]
[1-4] Department of Endocrine Surgery, King George's Medical University, Lucknow, Uttar Pradesh, India
Corresponding Author: Pooja Ramakant, Additional Professor, Department of Endocrine Surgery, King George's Medical University, Lucknow, Uttar Pradesh, India, e-mail: poojaramakant@gmail.com
Abstract: Rarely, clinical findings and imaging are unable to differentiate the non-thyroidal swellings from thyroid mass and surgeons may come across intra-operative surprise.
Keywords: Thyroid gland, anterior neck cysts

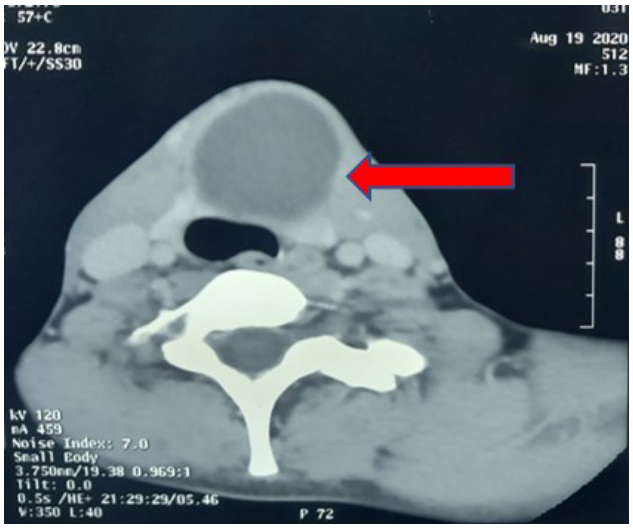
A number of non-thyroidal lesions like dermoid cyst, epithelial inclusion cyst, lipoma, pre-tracheal lymph nodes may mimic thyroid nodules (1) . Pre-operative work-up becomes crucial to differentiate the origin of the mass to avoid any iatrogenic damage to the thyroid gland during surgery. However, sometimes even clinical findings and imaging also cannot differentiate the non-thyroidal swellings from thyroid mass and surgeons may come across intra-operative surprise. We herein present a case of cystic lesion mimicking a thyroid swelling.

A 40 year male patient presented with an anterior neck swelling for the past 10 years, which was well defined and showed movement with deglutition (Figure 1). Radiologically, on both high resolution ultrasound and computed tomography of neck, a cystic lesion was visualised arising from the isthmus of thyroid in midline, measuring approximately 75x48x46mm, without any solid component or calcification (Figure 2). Fine needle aspiration cytology was also reported as Bethesda category II with scattered follicular epithelial cells and abundant colloid in background. Intra-operatively, a cystic lesion was visualised separate from the thyroid gland below the strap muscles (Figure 3). Final histopathology revealed a benign dermoid cyst showing pseudostratified columnar epithelium admixed with dense inflammatory infiltrate.

Cystic lesions in the anterior aspect of neck mimicking a thyroid swelling maybe epidermal inclusion cyst or a dermoid cyst, both of which are rare (2). High clinical suspicion with appropriate radiological investigations may help in distinguishing thyroid from non- thyroidal lesion, however, surgeons do come across intra-operative surprises, and hence meticulous dissection with careful handling of thyroid becomes mandatory.







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