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Incidental micropapillary carcinoma in thyroidectomy specimens and criteria employed for Diagnosis - A Retrospective Study

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Abstract
Incidental Papillary thyroid Microcarcinoma (I-PTM) is a tumor focus that is clinically unsuspected before thyroid surgery and is identified in the final pathological examination of a thyroidectomy specimen. Papillary thyroid Microcarcinoma has a benign behavior with excellent prognosis in most cases and therefore several controversies regarding the need for completion surgery for excision of remaining thyroid tissue and lymphnodes exist. A total of 22 patients with PTM incidentally diagnosed on postoperative histopathological examination of the excised thyroid tissue were analyzed for assessing the rate of incidental diagnosis of PTM and their demographic features and the surgical procedures used for their treatment. I-PTM was diagnosed in 13.6 % of males and 86% of females respectively. The average age in cases with I-PTM was 40 years (range 25 to 65 years). Of the 22 cases of I-PTM, 11 were operated with a pre-diagnosis of Multi nodular goitre and 8 were operated with a pre-diagnosis of solitary nodule (colloid nodule /follicular adenoma).Total thyroidectomy was performed in 11 cases,sub-total thyroidectomy was performed in 9 cases and right hemithyroidectomy was performed in 2 cases. In one case of I-PTM lower margin of excision was involved and was subjected for radioiodine therapy at referral centre.

Keywords: Micropapillary Carcinoma, Thyroidectomy, I-PTM

Introduction
Thyroid malignancy is the most common malignancy of the endocrine system with incidence of approximately 9/1,000,000 per year. The incidence of well differentiated thyroid carcinoma particularly Papillary carcinoma has been increasing since the last 20-30 years [1]. The surveillance epidemiologic and end results (SEER) database shows more than a two fold increase thyroid cancer since 1995. An important contributing factor for the increased incidence of such well differentiated cancers is the increasing diagnostic rates of Papillary thyroid microcarcinoma (PTM). Other factors such as iodination programmes in low iodine intake areas,detailed histopathological examination of the excised thyroid tissue and the increase in bilateral total excision of the thyroid gland during thyroid surgery have also been attributed to the increasing rates of large (> 10 cms) and micropapillary carcinoma [2].
Papillary thyroid Microcarcinoma (PTMC) is a specific group of Papillary thyroid carcinoma (PTC) and is defined by WHO on the largest diamension of 1.0 cm or less. Most PTMC are not detectable at clinical examination and are diagnosed incidentally during pathologic examination of thyroid specimens after surgery for benign thyroid tumors or in autopsies. If malignancy is not suspected clinically, tumors that are detected during the histopathological examination of specimen undergoing thyroidectomy surgeries are called Incidental and PTMC is the most common type of incidental thyroid carcinoma [3].
Incidental Papillary thyroid Microcarcinoma (I-PTM) is a tumor focus that is clinically unsuspected before thyroid surgery and is identified in the final pathological examination of a thyroidectomy specimen. Papillary thyroid Microcarcinoma has a benign behavior with excellent prognosis in most cases and therefore several controversies regarding the need for completion surgery for excision of remaining thyroid tissue and lymphnodes exist. The incidence of thyroid carcinoma in multi-nodular goiter (MNG) cases is reported to be 7.5-13 %. The diagnostic value of FNAC is low in the diagnosis of malignancy in MNG cases because of the presence of multiple nodules in MNG cases and many authors recommend Total thyroidectomy for non-malignant thyroid diseases such as MNG, C/c thyroiditis and Grave's disease [4].

Methodology

The objective of the study is to describe the incidence and clinical/pathological characteristics of I-PTM in an endemic goitre area. A retrospective analysis of patients who underwent surgical management of thyroid gland for different aetiologies at the medical college between January 2017 and December 2020 was performed. We excluded patients who underwent thyroidectomy for a diagnosis of carcinoma thyroid and also who had any of the following high risk characteristics pre-operatively as per 2015 American Thyroid association guidelines.

- Clinically apparent lymphnode metastasis
- Distant metastasis
- A history of radiation or a positive family history

Bilateral nodularity was not used as an exclusion criteria.

A total of 22 patients with PTM incidentally diagnosed on postoperative histopathological examination of the excised thyroid tissue were analyzed for assessing the rate of incidental diagnosis of PTM and their demographic features and the surgical procedures used for their treatment.

Histopathological parameters were established by microscopic criteria, including the size of PTM, location in the thyroid gland, multifocality and bilaterality in the thyroid lobes,thyroid capsule invasion, presence of lymphovascular invasion(LVI), lymphnode metastasis and tumor recurrence.

As an adjuvant treatment, analysed completion thyroidectomy or I-PTM cases with unilateral thyroidectomy, L-Thyroxin (LT4) treatment for the suppression of Thyroid stimulating hormone (TSH) and Radioiodine (RAI) treatment.

Results:

For the study period of about 3 years 329 thyroidectomies were performed in our center and 52 (15.5%) patients were diagnosed with a malignancy. Of these patients 5(10%) were diagnosed with follicular carcinoma, 2(5%) were diagnosed with anaplastic carcinoma and 44 (85%) were diagnosed with papillary carcinoma. Of the papillary carcinoma cases 15(35%) were diagnosed with classical papillary carcinoma and 29 cases (65%) were diagnosed with papillary microcarcinoma (tumor size 1cm or smaller). FNAC was not performed in 4 of the 29 papillary microcarcinoma cases and 3 cases were diagnosed with malignancy by FNA and this group was not included in the study. In this study the IPTM rate was 7% (22 cases).

I-PTM was diagnosed in 13.6 % of males and 86% of females respectively. The average age in cases with I-PTM was 40 years (range 25 to 65 years). Of the 22 cases of I-PTM, 11 were operated with a pre-diagnosis of Multi nodular goitre and 8 were operated with a pre-diagnosis of solitary nodule (colloid nodule /follicular adenoma).Total thyroidectomy was performed in 11 cases, sub-total thyroidectomy was performed in 9 cases and right hemithyroidectomy was performed in 2 cases. In one case of I-PTM lower margin of excision was involved and was subjected for radioiodine therapy at referral centre.

Table 1: Malignant tumors detected in thyroidectomy specimens

Malignancy	Total 52 (16%)
Anaplastic carcinoma	2 (5%)
Follicular carcinoma	5 (10%)
Papillary carcinoma	44(85%)
Classical	6 (35%)
Papillary microcarcinoma	11 (65%)
Incidental	22 (7%)

Table 2: Sex distribution of patients with surgical disease of the thyroid gland

Patients	Total	Male	Female
Thyroidectomy cases	329	19 (5.7)	310 (94 %)
I-PTM cases	22	3 (13.6 %)	19 (86%)
Rate of I-PTM	7%	15.7%	6.1%

Table 3: Age distribution of patients with surgical disease of the thyroid gland

Age distribution	**Patients with I-PTM*(%)**
21-40 years	11 (50%)
41-60 years	9 (41%)
61-80 years	2 (9 %)
The average age in cases of I-PTM was 40 years * Incidental Papillary Thyroid microcarcinoma	

Discussion

The ratio of IPTM is reported to be 7.1%–16.3% in the literature. The IPTM ratio in this study was 8.01%, which is consistent with the literature. In the literature, the ratio of incidental carcinomas among all papillary thyroid carcinomas is reported to be 49%–75.5%. In this study, the ratio of incidental carcinomas among all papillary thyroid carcinomas was 50 %. It is reported that the ratio of IPTM cases has increased in recent years and the increase in total thyroidectomies is a contributing factor. It is reported that the ratio of IPTM cases has increased in recent years and the increase in total thyroidectomies is a contributing factor. During our study period in the endemic area, the proportion of PTM was 65% among all papillary thyroid cancer cases, and a vast majority (75.8 %) of them showed incidental diagnosis, which indicates the importance of this pathology in the increasing rates of differentiated thyroid cancers. Lombardi *et al*. reported the proportion of I-PTM to be 42%, of which 75.5% were incidental in an area with a high prevalence of goitre. Rosa Pelizzo *et al* [5]. have also reported an increase in the proportion of PTM from 35% to 56%, of which 60% were incidental. In another study, the proportion of PTM in papillary thyroid cancer cases was determined to be 49%, of which 58% were incidental. The proportion of incidental cases among all PTM cases was found to be between 49% and 75.5%. Londero *et al* [6] recently reported that age-standardized rates increased from 0.35 per 100,000 per year in 1996 to 0.74 per 100,000 per year in 2008. About 59% of PTM cases were identified incidentally, and a significant rise in incidence was found only for the incidental cases [7-8].

The important properties of papillary thyroid microcarcinomas are multifocality and bilaterality. Multifocality is the presence of tumor in more than one focus in the same thyroid lobe or the presence of tumor in both lobes. In the literature, the multifocality rate in IPTM is reported to be 13%–41%. In this study, the multifocality rate was 9 % and the risk of cancer in the opposite lobe was 50% in patients with more than one focus in the same lobe. The

determination of multifocality in papillary microcarcinoma is difficult in the preoperative period. In this study, the rate of multifocality is lower than that reported in the literature. The reason for this variability is thought to be because of the use of different diagnostic criteria in different studies and may be because of the possibility of missing sight.

The increasing number of total thyroidectomies appears to be an important factor for the higher rate of incidental PTM. In our study, the incidence (11.6%) of I-PTM among total thyroidectomy cases was more than twice the incidence (5.5%) after hemithyroidectomy. Rosa Pelizzo *et al*. reported an increase in the proportion of total thyroidectomies (from 67% to 78%) and PTM (from 35% to 56%). The prevalence of PTM is higher in patients with bilateral surgery.

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Clinico-pathological Characteristics of Incidental Papillary Thyroid Microcarcinoma

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Abstract
More than ten microscopic variants of PTC have been documented. The most common variant is classical type PTC, which may also be referred to as typical PTC or usual type PTC. The majority of PTCs are of the classical type. Diagnosis is based on typical nuclear features, which should be present in tumour cells. Papillary structures are not present in all tumours. Psammona bodies are sometimes present. Surgically treated patients between January 2017 and December 2020 were retrospectively analysed. The study involved 329 surgical patients with benign disease of the thyroid, without any diagnosis of preoperative malignancy. Generally cells with nuclear clearing were arranged around the fibrovascular core in histopathological eaxamination. No lymphovascular invasion was detected in any of the cases. Other histopathological findings accompanying I-PTM were MNG in 7 cases (64%), lymphocytic thyroiditis in 4 cases (36%) and Hashimoto's thyroiditis in 1 case (9%).The mean size of the papillary thyroid foci was 5.7 mms.

Keywords: Incidental, Papillary Thyroid Microcarcinoma, MNG

Introduction
The thyroid gland is an endocrine organ located at the caudal part of the neck on the sides and in front of the trachea. The thyroid gland derives its name from the Greek word 'thyreos', meaning shield. The normal weight of the thyroid gland is between 15 and 25 g in adults [1]. Thyroid anatomy consists of lateral lobes, which are connected medially by the isthmus. The lobes are approximately 4 cm in length, 1 to 2 cm in thickness and 2 cm in width. The isthmus is located at the level of second to fourth tracheal ring and measures about 2 to 6 mm in thickness [2].

More than ten microscopic variants of PTC have been documented. The most common variant is classical type PTC, which may also be referred to as typical PTC or usual type PTC. The majority of PTCs are of the classical type. Diagnosis is based on typical nuclear features, which should be present in tumour cells. Papillary structures are not present in all tumours. Psammona bodies are sometimes present. Pseudoinclusions may be visible in nuclei, as well as nuclear grooves, as a sign for nuclear membrane folding. Due to chromatin margination tumour nuclei may resemble the "Eye of Little Orphan Annie", the character in the comic strip. Small PTCs sized 10 mm or less are categorized as PTC microcarcinomas [3-4]. The malignancy potential of these lesions is low and microcarcinomas are a frequent incidental finding in autopsy studies. If sub-millimeter carcinomas are included, the prevalence of PTC microcarcinomas may be as high as 35% in autopsy series. Follicular variant is the most common subtype of PTC after the classical type. It consists of follicles surrounded by cells with the typical nuclear features of PTC. The follicular variant of PTC has a comparable or more favourable prognosis than the classical type, but the typical papillary structures are rare or absent in tumours. A diffuse sclerosing variant of PTC occurs predominantly in young patients and has a diffuse growth pattern and dense sclerosis, but with typical PTC elements [5-6]. LN and distant metastases are more common than in the classical type, but the prognosis appears to be as good as in classical PTC. Tall cell, columnar cell and hobnail variants of PTC are rare but more aggressive tumours than classical PTC. The tall cell variant is a PTC subtype with tall cells, at least twice as high as they are long. A tall cell variant of PTC has a high risk of recurring and causing mortality.

Methodology

Surgically treated patients between January 2017 and December 2020 were retrospectively analysed. The study involved 329 surgical patients with benign disease of the thyroid, without any diagnosis of preoperative malignancy. Total thyroidectomy or hemithyroidectomy was performed for the treatment of benign thyroid diseases. A total of 22 patients with PTM incidentally diagnosed on postoperative histopathological examination of the excised thyroid tissue were analysed for assessing the rate of incidental diagnosis of PTM and their demographic features and the surgical procedures used for their treatment.

Histopathological parameters were established by microscopic criteria, including the size of PTM, location in the thyroid gland, multifocality and bilaterality in the thyroid lobes,thyroid capsule invasion , presence of lymphovascular invasion(LVI),lymphnode metastasis and tumor recurrence.

As an adjuvant treatment, analysed completion thyroidectomy or I-PTM cases with unilateral thyroidectomy, L-Thyroxin (LT4) treatment for the suppression of Thyroid stimulating hormone (TSH) and Radioiodine (RAI) treatment.

Follow-up: were done at a tertiary referral centre.

First and third month post-operatively. Biochemical analyses for Serum TSH and Thyroxin (FT4) were performed in order to determine the suppressive dose of LT4 (suppression of TSH at a level of <0.25 uIU /ml.

Sixth month post-operatively biochemical analyses for Serum TSH,FT4,Thyroglobulin (Tg) and Anti-thyroglobulin antibody (anti-TgAb) were performed in total thyroidectomy cases.An ultrasound scan of the cervical lymphnodes in all patients and the remaining lobe in hemithyroidectomy patients was also performed.

Yearly- An ultrasound scan of the cervical lymphnodes in all patients and the remaining lobe in patients with hemithyroidectomy was repeated. Biochemical analyses for Serum TSH, FT4, Tg and anti Tg Ab were performed.

Outcome:

Locoregional or distal recurrence of thyroid malignancy in the follow-up period and disease –free or overall survival of patients with I-PTM were the primary outcome parameters.

Results

Table 1: Clinicopathologic characteristics of Incidental papillary thyroid microcarcinoma (I-PTM)

Characteristics N=22(%)	
Tumor localization	
Right lobe	11(50%
Left lobe	8(36%)
Isthumus	1(4.5%)
Multifocal	2(9%)
Pre-diagnosis	
MNG	14(63%)
Solitary nodule	8(36%)
Surgical treatment	
Total thyroidectomy	11(50%)
Sub-total thyroidectomy	9(40.9%)
Hemi-thyroidectomy	2(9.1%)

Table 2: Size distribution of Incidental Papillary thyroid microcarcinoma (I-PTM) foci

Size	Right lobe	Left lobe	Isthumus %	%
0-3 mm	0	1	0	9%
4-6 mm	0	5	0	45%
7-10 mm	4	1	1	36 %
Total: 11. Mean size of foci is 5.7 mms.				

Generally cells with nuclear clearing were arranged around the fibrovascular core in histopathological eaxamination. No lymphovascular invasion was detected in any of the cases. Other histopathological findings accompanying I-PTM were MNG in 7 cases (64%), lymphocytic thyroiditis in 4 cases (36%) and Hashimoto's thyroiditis in 1 case (9%).The mean size of the papillary thyroid foci was 5.7 mms.

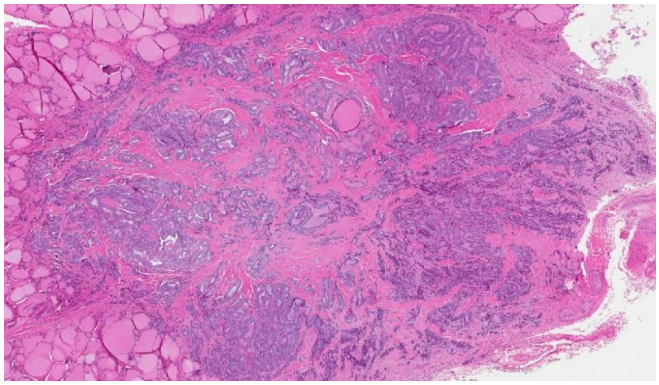

Fig 1: Papillary thyroid microcarcinoma showing an infiltrative pattern of growth measuring 5 mms in maximal diameter

Discussion

In general, incidental tumour foci are relatively smaller in size than nonincidental tumour foci. The average size of the tumour foci was <5 mm in patients with I-PTM. Our results confirmed the relatively small size (average5.7 mm) of the tumour foci in the thyroid glands of patients with incidental PTM, of which 54% of foci were ≤6 mm. A study reported that the tumour foci were ≤6 mm in 83% of such patients.[7] Previous studies have reported tumour size as a risk factor for lymph node metastasis and recurrence.[8] In general, tumour foci diameter >5 or 6 mm has appeared as an independent risk factor. Therefore, patients with foci >6 mm in diameter should be followed up more closely. The recurrence rate of PTM is very low even among tumour foci > 6 mm, which has been reported to range from 0% to 5%.

In our endemic goitre area, diagnosis of I-PTM in thyroid tissue is not an uncommon situation after thyroid surgery for benign diseases. The prevalence of I-PTM increases parallel to the increase of total thyroidectomy rate for benign thyroid diseases. Multifocality and bilateralism are main pathologic features of PTM. Size of I-PTM foci in thyroid tissue is relatively small and the majority are smaller than 6 mm. Small foci of PTM create very low risk of lymph node metastasis and locoregional or distant recurrences in the follow-up period. The prognosis is exczllent after surgical treatment and TSH suppression with LT4 administration. Routine adjuvant surgical and nuclear treatment as

completion thyroidectomy, lymph node dissection, and RAI application is unnecessary in vast majority of patients due to low risk of recurrence. Such adjuvant procedures should be reserved for small number of recurrent cases discovered in the follow-up period.

Conclusion

Other histopathological findings accompanying I-PTM were MNG in 7 cases (64%), lymphocytic thyroiditis in 4 cases (36%) and Hashimoto's thyroiditis in 1 case (9%).The mean size of the papillary thyroid foci was 5.7 mms.

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Histopathological Features of Leprosy: Descriptive Study

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Abstract

Introduction: The histopathology of lepromatous skin varies according to the cell-mediated immunity of the host against *Mycobacterium leprae*. In tuberculoid and borderline tuberculoid leprosy, epithelioid noncaseating granulomas predominate, and acid-fast bacilli (AFB) are absent or only rarely present. In borderline lepromatous and lepromatous leprosy, the infiltrate is composed of macrophages with a vacuolar cytoplasm, lymphocytes, and plasma cells. *Methodology:* A Descriptive study was carried out at a Tertiary care Hospital to know the in depth features of Leprosy. Totally 58 cases were recruited based on non probability purposive sampling technique. *Results:* Borderline tuberculoid (BT) comprised 33 cases (56.8%), Tuberculoid leprosy (TT) 20 cases (34%), Borderline leprosy 1 case (1.7%) and Borderline lepromatous (BL) 4 cases (7.3%). One case of BT was in reaction and three were of relapses. *Conclusion:* There is no independent gold standard for diagnosis of leprosy.

Keywords: Leprosy; Histopathology; Laprae.

Introduction

The world granuloma was originally used to describe the mass of granulation tissue ie., capillaries, fibroblasts and macrophages which forms at a site of tissue repair. This regrettable definition has probably been handed down from Virchow (1964) [1] who defined a granuloma as essentially a tumor or neoplasm composed of granulation tissue. Fobus (1955) [2] has emphasised that the process of granulomatous inflammation is intimately connected with activity on the part of the macrophages. More recently the word granuloma is considered as a broad term covering subacute to chronic inflammatory processes that are more or less circumscribed. Histologically one sees a varying assortment of epithelioid cells, histiocytes, giant cells of different types, lymphocytes, plasma cells, eosinophils and mast cells at times with zones of necrosis of pesudonecrosis (Montgomery, 1967) [3]. A contemporary definition of a granuloma is a lesion consisting predominantly of macrophages. It need not necessarily show necrosis, fibrosis or giant cells. More recently a granuloma is defined as a collection of histiocytes that may have abundant cytoplasm and confluent borders (epithelioid histiocytes), often with Langhan's type giant cells. Granulomas may be associated with necrosis, may palisade around areas of necrobiosis, may be mixed with other inflammatory cells, may include foreign body-type giant cells, and may contain ingested foreign material or pathogens (Lever, 1997) [4].

The histopathology of lepromatous skin varies according to the cell-mediated immunity of the host against *Mycobacterium leprae*. In tuberculoid and borderline tuberculoid leprosy, epithelioid noncaseating granulomas predominate, and acid-fast bacilli (AFB) are absent or only rarely present. In borderline lepromatous and lepromatous leprosy, the infiltrate is composed of macrophages with a vacuolar cytoplasm, lymphocytes, and plasma cells. AFB is numerous. Edema inside and outside the epithelioid granulomas, together with the appearance of large giant cells, are the main features of type 1 reactions. A conspicuous neutrophilic infiltrate in the subcutis

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with or without vasculitis is found in erythema nodosum leprosum. The main histopathologic features of leprosy and its particular forms are discussed in this review.

The main feature of the vast majority of leprosy biopsy specimens is a granulomatous infiltrate that has different features according to the form of leprosy, the time and site of the biopsy, the presence of a leprosy reaction, and therapy. The clinical spectrum of leprosy correlates in most of cases (but not in all) directly with histopathologic results, reflecting the different grade of cell-mediated immune response (CMI) of the host against *Mycobacterium leprae* [5-8].

Methodology

A Descriptive study was carried out at a Tertiary care Hospital to know the in depth features of Leprosy. Totally 58 cases were recruited based on non probability purposive sampling technique.

These patients are clinically suspected of having granulomatous and non-granulomatous lesions. The duration of their illness varied from months to years and the patients belonged to a wide age range. The clinical assessment of the patients were done by the Dermatologists. The skin biopsies were taken from the most prominent lesion or from the anaesthetic area depending on clinical diagnosis. These sections were subjected to microscopic examination and the study of the epidermis, dermis, dermal appendages, arteries and nerve bundles were carried out.

Results

This study was undertaken to evaluate skin biopsies showing granulomatous reactions in detail. Of the 94 cases evaluated, 58 were of leprosy. In the rest of the cases, the aetiologies were of fungi, tuberculosis and non-infections granulomas. Cases of leprosy were classified according to Ridley and Joplings classification and the borderline tuberculoid leprosy comprised the largest group coming upto 56.8%. There were 11 cases of cutaneous tuberculosis, among this lupus vulgaris comprised 7 and tuberculosis verucosa cutis 4 cases. All the cases of leprosy and tuberculosis were subjected to AFB staining. For leprosy cases modified Fite-Faraco stain was used.

Borderline tuberculoid (BT) comprised 33 cases (56.8%), Tuberculoid leprosy (TT) 20 cases (34%), Borderline leprosy 1 case (1.7%) and Borderline lepromatous (BL) 4 cases (7.3%). One case of BT was in reaction and three were of relapses.

A diagnosis of spectrum of leprosy was made when the granulomas were compact and composed of epithelioid cells, surrounded by a dense cuff of lymphocytes with or without Langhans giant cells or in the presence of erosion of epidermis .

The diagnosis of BT spectrum of leprosy was made when the granuloma was less compact and epithelioid cells were admixed with lymphocytes. The cuffing of granuloma by lymphocytes was less pronounced .

One case of BT was in type-1 reaction, which was diagnosed by oedema in granuloma, dilated lymphatic channels and infiltration of the granuloma by acute inflammatory cells . Three cases of BT were of relapses, where the patients had full course multi-drug chemotherapy earlier. In two of them recurrence occurred 2 years after completion of therapy and in one it occurred after 1 V. years. BB spectrum of leprosy was diagnosed when the granulomas were composed of sheets of epithelioid cells with scanty lymphocytes.This type of picture was obtained in 1 patient. BL spectrum of leprosy was diagnosed when the 4uloma was composed of macrophages admixed with a considerable number of lymphocytes.

Discussion

Out of 58 cases of leprosy, 12 cases showed acid fast bacilli (20.6%). Thisis comparable to a study by Prasad et al (1997) who studied 49 cases of leprosy theskin was multibacillary in 1 1 cases (22.6%).

When Job CK et al [9] studied 26 patients Acid fast bacilli was seen in thesections of only two cases. In the same study, M. leprae were detected using" PCR technique in 1 1 patients. It is included that since the ûnding of M- leprae is crucialin the conûrmatory diagnosis of early leprosy and acid fast bacilli was demonstrable only in a limited number of cases, it is suggested that other methodsfor detection of M. leprae such as PCR should be employed whenever feasible.

In the present study, Job and Chacko" modiûcation of File Faraco stainingwas used for the demonstration of bacilli. One of the main drawbacks of theconventional File Faraco Stain for M. leprae that the decolourisation step is veryfast, as acid alcohol is used for the purpose. Since M. leprae is less acid andalcohol fast, if declorisation step is prolonged for a few seconds more, the bacilliwill not be demonstrable. On the other hand if decolourisation is not enough, thebackground will be densely stainedand it may be difficult to identify the acid

fastbacilli. This dificulty is overcome in this modification. In this method instead of 1% acid alcohol, only 5% sulphuric acid is used, so the decolourization time can beprolonged upto 10 minutes. In the AFB stained sechlinnthe 1-2 micrometer Mdfast granules in eccrine sweat gland cell could be used as a satisfactory intimal positive control.

The AFB staining was also useful in demonstrating mast cells in skin andnerve sections. Ridleygé has observed an increase in mast cells which in somecases is confined to sites like nerve. Lin et al have also observed an increase inmast cells in indeterminate leprosy- In the present study also the increase in mastcells was noted in skin sections. Under low power objective there is a chance tomistake mast cell granules for M. leprae- In order to avoid this all the AFB stainedsections should be examined under oil immersion objective.

Most consistent ûnding in all cases of leprosy was the selective localization and infiltration of neurovascular bundles by the granulomas. Also there was often epidermal atrophy, lack of caseation necrosis and lack of fibrosis. Epidermalatrophy was more pronounced in case of 'IT granulomas.

Nirmala V [10] et al had made a comparison between tuberculoid leprosy andcutaneous tuberculosis and noted that in tuberculosis there is often a proliferationreaction of the epidermis with areas of ulceration, signiûcant ûbrosis and absence of nerve destruction.

A review of literature (Ridley and Jopling)" indicates that the lymphocyteswere very numerous in TI' polar and are peripheral to the epithelioid cellaggregates, forming a dense cuff around it. In BT the number of lymphocytes isvariable and is often present within the granuloma rather than peripheral to it. In BB spectrum the lymphocytes were few. All these findings were confirmed in this study and the BB granulomas alsoshowed a plasmacytic infiltration in addition to the lymphocytes. Giant cells within the granulomas were variable and were most numerousin the TT granulomas, only a few BT cases showed them and was absent in BBand BL ones. In the Ridley and Joplings original article it is suggested thatconsiderable number of large Langhan's giant cells throughout the granuloma inthe superficial dermis signify TT polar. Giant cells are fewer in TT subpolar. InBT granuloma, giant cells may be fairly numerous, but though of the Langhan's type, they are not very large.

Also it was noted that, in 'IT spectrum the granulomas were compact andmost frequent in the superûcial dermis often with associated epidermal atrophy. In contrast, BT granulomas were less compact, showed distribution following neurovascular bundles. These observations parallels with that made byauthors like Lever and Rid ley.

As there can be some degree of overlap between different types of leprosy,both clinically and histopathologically. Correlation of clinical and histopathological features along with bacteriological index appears to be more useful for accuratetyping of leprosy than considering any oneof the single parameters alone. Taking any of the clinical signs, clinical types, histopathological parameters orhistopathological types as a gold standard is not ideal.

Conclusion

Correlation of clinical and histopathological features along with bacteriological index appears to be more useful for accurate typing of leprosy than considering any one of the single parameters alone.

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A Study on Histopathological Features of Granulomatous Lesions of Skin

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Abstract

Introduction: The morphologic pattern in the various granulomatous diseases may be sufficiently different, to allow reasonably accurate diagnosis by an experienced pathologist, however there are so many atypical presentations, that it is always necessary to identify the specific etiologic agent by special stains for organisms, by culture methods and by serological studies to exclude an infectious cause. *Methodology:* The clinical assessment of the patients were done by the Dermatologists. The skin biopsies were taken from the most prominent lesion or from the anaesthetic area depending on clinical diagnosis. *Results:* Leprosy formed the largest population, of the total 58 cases were Leprosy. The next in frequency was fungal granulomas. Out of the total 13 cases, in 9 cases (69.2%), a diagnosis of chromoblhomycosis was made, in one case the diagnosis was Histoplasmosis (7.7%). *Conclusion:* A detailed evaluation of good H&E stained sections could offer many diagnostic points for the accurate aetiological classification

Key words: Granulomatous; Histopathology; Leprosy.

Introduction

Granulomatous inflammation is a distinctive pattern of chronic inflammatory reaction in which the predominant cell type is an activated macrophage with a modified epithelial-like (epithelioid) appearance. Recognition of the granulomatous pattern in a skin biopsy specimen is important because of the limited number of possible conditions that cause it and the significance of the diagnosis associated with the lesion [1]. A granuloma is a microscopic aggregation of macrophages that are transformed into epithelium-like cells, usually surrounded by a collar or mononuclear leucocytes principally lymphocytes and occasionally plasma cells. Granulomatous dermatitis is defined as a predominantly dermal, chronic inflammatory reaction in which formed granulomas are present. Conditions in which there is a diffuse infiltration of histiocytes within the dermis, such as lepromatous leprosy are not included in this reaction pattern [2].

It is difficult to present a completely satisfactory classification of the granulomatous reaction. Five histological types of granulomas can be identified on the basis of the constituent cells and other changes within the granulomas as — sacoidal,luberculoid, necrobiotic, suppurative and foreign body.

The morphologic pattern in the various granulomatous diseases may be sufficiently different, to allow reasonably accurate diagnosis by an experienced pathologist, however there are so many atypical presentations, that it is always necessary to identify the specific etiologic agent by special stains for organisms (eg., acid fast stains for mycobacterium), by culture methods (eg., in fungal causes) and by serological studies (eg. in syphilis) to exclude an infectious cause. There have been considerable advances made in the understanding of the formation and maintenance of granulomas in tissue reaction and the roles played by B and T lymphocytes and cytokines. The different types of multinucleate giant cells seen in grahulomas may simply reflect the types of cytokines being produced by the component cells.

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This new information has not so far been shown to be useful in routine diagnostic problems. Polymerase chain reaction (PCk) have proved useful in detecting in fectioills agents in tissue sections, particularly mycobacterial species [3,4].

Methodology

The biopsy material for the study was obtained from the Department of Dermatology, Medical College. Ninety-four cases showing a granulomatous reaction pattern in the skin biopsy were selected. These patients are clinically suspected of having granulomatous and non-granulomatous lesions. The duration of their illness varied from months to years and the patients belonged to a wide age range. The clinical assessment of the patients were done by the Dermatologists. The skin biopsies were taken from the most prominent lesion or from the anaesthetic area depending on clinical diagnosis. Both scalpel and punch biopsy specimens are included in the study. Specimens were fixed in 10% formalin for 7-8 hours and are processed. Sections of about 41.tm thickness were taken and stained with H & E.

These sections were subjected to microscopic examination and the study of the epidermis, dermis, dermal appendages, arteries and nerve bundles were carried out.

Results

Age of the patients ranged from 13 years to 85 years, with a mean age of 76.7 years. Out of the 94 patients, 63 were males and 31 were females.

Considering the distribution of aetiological factors — leprosy comprised the largest group coming up to 61.7% of the total number of cases. Tuberculosis

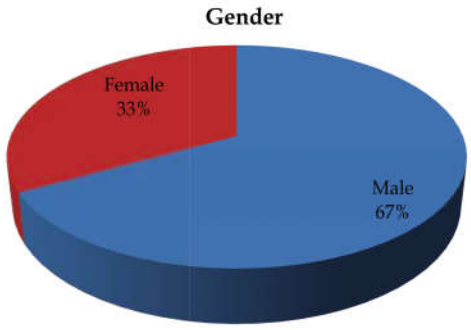

Fig. 1: Gender distribution

comprised 11.7% and fungal comprised 13.8%. The remaining was of diverse aetiology which comprised 12.7%.

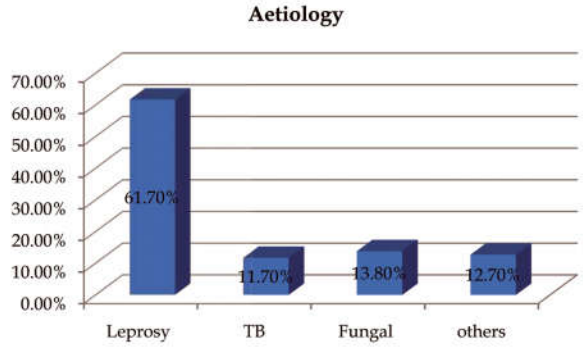

Fig. 2: Aetiology distribution

Leprosy formed the largest population, Of the total 58 cases were Leprosy. The next in frequency was fungal granulomas. Out of the total 13 cases, in 9 cases (69.2%), a diagnosis of chromoblhomycosis was made, in one case the diagnosis was Histoplasmosis (7.7%). Rest of the 3 cases (23%) failed to show any fungal hyphae or spores and the diagnosis was given as suppurative granulomas suggestive of fungal aetiology Considering cutaneous tuberculosis, of the total 11 cases, lupus vulgaris (LV) comprised 7 cases (63.6%) and the rest were of tuberculosis verucosa cutis (TBVC) (36.3%).

Table 1: Fungal Granulomas

Fungal granuloma	Chomoblasto-mycosis	Histoplasmosis	Others
Total: 13	9	1	3

Table 2: Miscellaneous

Miscellaneous (d)	Number	Percent
Granuloma anulare	6	50
Foreign body reaction	3	25
Rheumatoid nodule	2	16.6
Parasitic granuloma	1	8.3
Total	12	

In the miscellaneous group, of the 12 cases, 6 cases were of granuloma anulare (50%), 3 cases were of foreign body granulomatous reaction(25%), 2 cases (16.6%) were of rheumatoid nodule and 1 case (8.3%) was of parasitic granuloma.

Discussion

This study was intended to analyze the histological features ingranulomatous lesions of the skin. The study was based 'mainly on a detailedmorphological analysis of skin biopsies with the use of the relevant special stains. It was hoped that this would pick up a recognizable aetiological factor in most, notif all the cases.

The features suggestive of the aetiology were well marked in many cases.Special stains were shown to be complementary in determining the aetiology.The various causes of cutaenous granulomas in this series as judged by thehistopathological features and is considered under four categoriesa,b, c and d.

In a similar study [5], the total number of cutaneous granulomas was 78, with minimum number of leprosycases (56.7%) followed by cutaneous tuberculosis, sarcoidosis, necrobiosislipodica, granuloma anulare, syphilis, mycotie granuloma and jumenilexanthogranuloma which constituted 1.25% each.

In the present study, out of the 94 patients the aetiological distribution wasalmost similar, but the number of fungal granulomas formed an outstanding ûgureconstituting 12.1%.

In 35% cases, the granulomas were of fungal aetiology coming second infrequency. As mentioned earlier this constituted a high ûgure comparing tosimilar studies and the disparity may be related to the high prevalence ofagricultural workers in the locality. Chromoblastomycosis which constituted 69.2% of the fungal granulomas; andpercutaneous inoculation of the fungus is the most widely accepted mode ofinjection.

Chromoblastomycosis is a chronic fungal infection of the skin andsubcutaneous tissues caused by demaliaceous fungi. All the cases were presentedas vermcous lesions and in most of them ven-ucous carcinoma was a clinicaldifferential diagnosis. Duration of the lesions ranged from 1-14 years and the most frequent site affected was the lower leg and foot.

One was a case of repeat biopsy, previous biopsy report was a Lupusvulgaris, but the patient failed to respond to anti-tuberculous regimen and a repeatbiopsy was taken.

According to Caplan RM (1988) [6] epiderrnoid carcinoma can arise inextensive chromoblastomycosis. If not diagnosed earlier, chromoblastomycosis can have a chronic evolutional course. By Minottoet al [7], chronicchromoblastomycosis can pose many problems such as difûculty in managingtherapy because of the recmdescent character of the disease, potential associationwith the growth of epidermal carcinoma in affected regions, and poor quality oflife and work incapacity to the patient.

In a study of 51 cases of chromoblastomycosis in Mexico by Bonifaz A et al [8] the principal aetiologic agent isolated was Fonsecaeapedrosi (90%). In our set up histopathological detection of sclerotic bodies was taken as conûrmatory andcultural isolation of the fungus was not attempted in most of the cases.

In one case the diagnosis was Histoplasma-capsulatiom. The patient was a 60 year old male when presented with multiple ulcers of duration ranging from 6months to 2 years. Ulcers were present on the angle of the mouth, dorsal aspect ofthe tongue and over the prepuce.

Tissue smears were negative for LD and Donovan bodies. We received biopsies from lesion on the angle of mouth and from tongue- Skin biopsy showed a chronicgranulomatous reaction with multiple rounded bodies inside the histiocytes. Thesespores were positive for PAS and Methenamine silver. Biopsy from the tongueulcer also showed a similar picture. A diagnosis of chronic disseminatedhistoplasmosis was made and the patient put on Itraconazole 300 mg/ day. Heresponded well with healing of the ulcers within 4 weeks. From review of literature, the largest endemic focus of histoplasmosis is inthe central eastern United States, it is a rare disease in India.

In the pre-AIDS era disseminated histoplasmosis was rare and thecutaneous manifestations thereof were reported infrequently. According to Goodwin[9], before the advent of HIV, disseminated histoplasmosis developed in only in 50,000 infections and was usually found ininfants, in patients with lymphoma or in those receiving immunosuppressivetreatment. Now it is the most common opportunistic infection in AIDS patientsliving in highly endemic areas .

Goodwin Jr et al [9] observed that cases with mild degrees of parasitizationpresents as chronic disseminated disease with multiple focal destructive lesionsand the response to treatment is generally good.

The number of patients belonging to this histopathological category was l 1.7%. In this study the diagnostic features of cutaneous tuberculosis included aproliferative reaction of the epidermis with areas of ulceration, presence of nearlyconûuent granulomas throughout the dermis and occasionally caseous necrosis inthe granulomas. Absence of nerve involvement proved a helpful feature todifferentiate from tuberculoid leprosy. Also there was signiûcant

increase indermal ûbrosis with increase in reticulin particularly in cases of long duration.

Nirmala V et al (1977) [10] suggests that the most important differentiatingfeatyure of cutaneous tuberculosis was a proliferative reaction of the epidermiswith absent nerve destruction.

According to Lever (l997) [11], the secondary epidermal changes in lupusvulgaris ranges from atrophy, ulceration, acanthosis or pseudoepitheliomatous hyperplasia. In the case of TBVC, the changes were more consistent and showedonly hyperkeratosis, acanthosis and papillomatosis; no epidermal atrophy wasobserved in these cases. .

In this study, all the cases of TBVC showed hyperplastic changes in theepidermis. The epidermal changes in lupus vulgaris vary from atrophy andulceration to hyperplasia.

Conclusion

Cutaneous granulomas can be of varied aetiology. Hence the task lies on the 'Dermatopathologist' to confirm and classify granulomas accurately for institution of proper therapy.

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