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Original Article

Indian Journal of Pathology: Research and Practice

Thermoregulation and Thermal Perception in Diabetic Peripheral Neuropathy: A Pathophysiological Perspective of Evaluation and Management

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Abstract

Background: Thermoregulation and thermal perception was considered as two independent processes involved with perceiving hot or cold stimuli which reflected small-fiber dysfunction in diabetic peripheral neuropathy (DPN). **Objective:** To explore and synthesize the existing evidence for thermoregulation and thermal perception for their testing and treatment methods in DPN from a pathophysiological perspective. **Methods:** A systematic review of PubMed, CINAHL and Google scholar was done using search terms "thermoregulation, thermal-hot/cold" to identify relevant citations for their inclusion after a three-level scrutiny for data extraction and descriptive synthesis into evaluation and management. **Results:** Of the total 30 included studies, 16 studies were on thermoregulation (body temperature=4, cold immersion recovery=1, warm immersion recovery=1, bronchial cold reactivity=1, cold pressor response=1, heat evoked potentials=2, thermal biofeedback=1, thermography/thermometry=3, device-specific use=2) and five studies were on thermal perception thresholds, one study on cooling detection thresholds and one study on heat pain thresholds. There were seven studies on interventions (cucumin=1, lycopene=1, quercetin=1, resveratrol=1, tapentadol=1, bone marrow transplantation=1, trolox=1). **Conclusion:** Thermoregulation and thermal sensory perception were altered in DPN, which was evidently demonstrated as changes in temperature, responses to immersion, heat evoked potentials, thermal perception thresholds, and thermal pain thresholds during assessment, and was positively reflecting therapeutic effects, efficacy and effectiveness of variety of interventions.

Keywords: Thermoregulation; Thermal sensory examination; Thermoreception; Diabetic neuropathy.

Introduction

Pain was the first and foremost sensory perception emphasized over the years of

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scientific development in the field of Medicine and healthcare.[1] In 1890s, neuroscientific observations of impaired temperature sensation together with that of pain had led to the supposition that the two sensations had a common anatomical pathway.[2]

Subsequently, thermal and non-thermal factors[3] and their role in bodily mechanisms for temperature control was gaining priority studying the influence of human circadian rhythms,[4] serotonergic system,[5] and central nervous system.[6] Then the emphasis undertook a shift from studies on thermoregulation and thermoregulatory mechanisms differentiating general and local temperature,[7] and neurophysiological evidence directed emphasis on thermal sensation as playing a vital role in health and disease.[8]

Later, the independent roles of temperature and thermal perception in the control of human thermoregulatory behavior was understood from a behavioral role of perceiving thermal sensation and thermal discomfort.[9] The importance of evaluating thermal sensation as one among the protective sensations arose from the incidence of accidental burns due to sensory deficits in hands/feet among people with peripheral nerve injuries.[10]

Anecdotally, thermal sensation was evaluated in the bedside neurological examination by touch, contact with objects and differentiating into hot/cold which were prone for huge inter-individual variability from a multifactorial viewpoint: patient-specific, therapist-specific and disease-specific.[11] Initial attempts to use visual analogue scales for quantifying self-rated thermal sensation was too subjective[12] for continuing its use for practice.

Quantitative sensory testing (QST) is objectified measurement method for evaluating sensations including touch, temperature, vibration, pressure, pain and two-point discrimination.[13,14] German Research Network on Neuropathic Pain (DFNS) had reiterated the importance of assessment of thermal sensation and thermal perception and thermal pain thresholds as part of routine QST15 for evaluation of small fiber dysfunction.[16]

"Clinically, QST may be useful for 1) the identification of subgroups of patients with different underlying pain mechanisms; 2) prediction of therapeutic outcomes; and 3) quantification of therapeutic interventions in neuropathic pain therapy."[17] In patients with primary complaints of neuropathic pain, QST can be used to determine detection, pain thresholds and stimulus-response curves and can thus detect both negative and positive sensory signs, the second ones not being assessed by other methods.[18]

Compared to regular clinical examination, QST could detect more abnormalities much earlier in the course of diabetic polyneuropathy and hence could aid as a valuable evaluation tool.[19] In diabetic peripheral neuropathy (DPN), the most intolerable symptom for patients is pain, which was not predicted by small-fiber dysfunction measured using QST. [20]

Identifying loss of protective sensation such as thermal sensation and/or thresholds on the plantar aspect of foot[21] and appropriately defining distal symmetric sensorimotor polyneuropathy[22] would enable early and appropriate delineation of high-risk or risk for ulceration[23] and lower extremity amputations[24] in feet of diabetic individuals.

Thus the objective of this study was to explore and synthesize the existing evidence for thermoregulation and thermal perception for their testing and treatment methods in DPN from a pathophysiological perspective.

Methodology

A systematic review of PubMed, CINAHL and Google scholar was done using search terms "(cold [Title] OR cooling [Title] OR temperature [Title] OR thermal [Title] OR heat [Title] OR hot [Title] OR warmth [Title] OR warm [Title]) AND (diabetes [Title] OR diabetic [Title]) AND (neuropathy [Title] OR neuropathic [Title])" to identify relevant

citations for their inclusion after a three-level scrutiny (title, abstract and full-text) for data extraction and descriptive synthesis into evaluation and management studies.

Results

Of the total 30 included studies, 16 studies were on thermoregulation (body temperature=4, cold immersion recovery=1, warm immersion recovery=1, bronchial cold reactivity=1, cold pressor response=1, heat evoked potentials=2, thermal biofeedback=1, thermography/thermometry=3, device-specific use=2) and five studies were on thermal perception thresholds, one study on cooling detection thresholds and one study on heat pain thresholds. There were seven studies on interventions (cucumin=1, lycopene=1, quercetin=1, resveratrol=1, tapentadol=1, bone marrow transplantation=1, trolox=1).

Thermoregulatory function

Body temperature

Bagavathiappan *et al*[25] assessed the correlation between plantar foot temperature and diabetic neuropathy using a non-invasive infrared thermal imaging technique in 112 subjects who had VPT > 20V and they found that DPN patients had a higher foot temperature (32-35^{0}C) compared to patients without neuropathy (27-30^{0}C). Mean foot temperature (MFT) showed a positive correlation with right and left great toe VPT values.

Naicker *et al*[26] undertook a cross-sectional study to identify risk factors for diabetic neuropathy and the association between foot temperature and development of diabetic neuropathy by studying 134 diabetic patients with peripheral neuropathy. Low foot temperature was not significantly associated with development of diabetic neuropathy which indicated that foot temperature alteration was merely an effect of autonomic neuropathy attributable to co-existing peripheral arterial disease.

Boyko *et al*[27] re-examined the association between skin temperature and autonomic neuropathy in a cross-sectional study of 712 veterans with diabetes mellitus. An infrared surface scanner was used to measure foot skin temperature at multiple sites. Subjects with sensory neuropathy had lower mean plantar foot skin temperature than those without (28.4^{0}C vs. 28.9^{0}C). Their results suggested that skin temperature might be slightly lower with higher orthostatic blood pressure fall in diabetic veterans.

Papanas *et al*[28] evaluated foot temperature in 30 type 2 diabetic patients with vs. 30 patients without peripheral neuropathy. Dorsal and plantar foot temperatures were significantly higher in group with neuropathy than in group without neuropathy.

Kitamura *et al*[29] studied 36 non-diabetic patients (control group) and 27 diabetic patients (diabetic group) undergoing elective abdominal surgery using standard non-invasive autonomic tests (heart rate variation at deep periodical breathing, Valsalva maneuver, and head-up tilt). The core temperature of the diabetic patients with autonomic dysfunction was lower from 120 min (35.1^{0}C) onward compared with the diabetic patients with normal autonomic function. The current study results indicated that diabetic autonomic neuropathy was associated with more severe intraoperative hypothermia.

Cold immersion recovery test

Bharara *et al*[30] investigated the effectiveness of testing cold immersion recovery responses in the diabetic foot with neuropathy using a contact thermography system based on thermochromic liquid crystals in 81 subjects with no history of diabetic foot ulceration who were assigned to neuropathy, non neuropathy and healthy groups. Patients with diabetes with neuropathy show the highest 'delta temperature', that is difference between the temperature after 10-minute recovery period and baseline temperature measured independently at all the three sites (first metatarsal head (MTH), second MTH and heel).

Warm immersion recovery test

Bharara *et al*[31] presented results of warm immersion recovery test in the diabetic foot with neuropathy using a liquid crystal-based contact thermography system in 81 subjects who were assigned to one of three study groups, that is diabetic neuropathy, diabetic non neuropathy and non diabetic healthy. Local measurements at the most prevalent sites of ulceration, that is metatarsal heads, great toe and heel, show highest temperature deficit after recovery for diabetic neuropathy group.

Bronchial cold reactivity

Heaton *et al*[32] compared five diabetic patients with severe symptomatic autonomic neuropathy, five diabetic patients without autonomic neuropathy and five non-diabetic controls for their responses to bronchial provocation testing with cold air. The first group did not show a significant fall in specific airways conductance, whereas conductance fell in the second group by 30.8% and in the third group by 22.7%.

Cold pressor test

Sayinalp *et al*[33] applied the cold pressor test to a group of 33 diabetic patients and 15 healthy controls. The mean diastolic cold pressor response was significantly lower in diabetic patients as compared with the control group.

Heat-evoked potentials

Chao *et al*[34] investigated the diagnostic role of Contact heat-evoked potential (CHEP) to record cerebral responses of A δ fiber-mediated thermonociceptive stimuli in 32 type 2 diabetic patients with skin denervation and neuropathic pain. Abnormal CHEP patterns (reduced amplitude or prolonged latency) were noted in 81.3% of these patients. The CHEP amplitude was the most significant parameter correlated with IENF density and pain perception to contact heat stimuli.

Wong and Chung[35] compared contact heat evoked potential (CHEP) parameters between healthy adults and diabetics with and without lower limb symptoms and found a significant difference in N1-P1 amplitude in the three groups after stimulation of the dorsum of the foot and the point 10 cm proximal to the lateral malleolus. CHEP thus could help to detect early A-delta fiber damage in diabetic patients with minimal neuropathy.

Thermal biofeedback

Fiero *et al*[36] examined association of nerve function with four common types of diabetic neuropathy (sympathetic-autonomic, vagal-autonomic, sensory, and motor) on 24 participants with diabetes mellitus (19 with type II and 5 with type I) whose hand temperature, foot temperature, and electrodermal gradient at the toes were monitored across six thermal biofeedback sessions. Participants were able to significantly raise foot temperatures across sessions, an average of 2.2^0 F, with lower-extremity sympathetic-autonomic and sensory neuropathies interfering with foot warming.

Thermography and thermometry

Bharara *et al*[37] emphasized on applications of thermography and thermometry in lower extremity wounds, vascular complications, and neuropathic complications which had progressed as a result of improved imaging software and transducer technology. The authors reviewed thermal measurement techniques specific to diabetic foot such as electrical contact thermometry, cutaneous thermal discrimination thresholds, infrared thermography, and liquid crystal thermography.

Fushimi *et al*[38] studied the thermographic patterns of 62 patients, who demonstrated contralateral leg vasodilatatory response to warm water immersion indicative of sympathetic neuropathy, using Thermoviewer MDJTG-MD. The thermographic pattern was found to be closely related to microangiopathy, R-R interval variation and motor nerve conduction velocity, with excellent reproducibility and required simple and non-invasive techniques.

Sundkvist *et al*[39] assessed the relationship between neuropathy and peripheral circulation (thermography) in 26 patients with a short to moderate duration (less than 20 years) and in 26 patients with a long duration (more than 20 years) of diabetes mellitus. The authors found a markedly delayed toe temperature increase after cooling followed by indirect heating occurred in diabetics of short duration with autonomic neuropathy (AN).

Device-specific use

Viswanathan *et al*[40] determine the effectiveness of Tip-therm, a temperature discriminator, in making an early diagnosis of distal symmetrical polyneuropathy in 910 diabetic patients and found that Tip-therm appeared to be an inexpensive, highly sensitive, and specific device for detection of diabetic neuropathy when compared with biothesiometry and a monofilament.

Arezzo *et al*[41] reported use of Thermal Sensitivity Tester (TST) and determined its normative values of threshold for detecting the colder surface using a two-alternative, forced-choice algorithm. The mean threshold in the normal population was found to be 0.67^0C and 1.01^0C for the index finger and great toe, respectively.

Thermal perception thresholds

Løseth *et al*[42] determined if neuropathy in diabetic patients could be detected by measurements of thermal thresholds, and compared the differences in parameters between 22 patients with and 37 patients without neuropathic symptoms. Thermal thresholds were significantly elevated (more abnormal) in patients with symptoms compared to controls, but only for cold perception threshold (CPT) in the asymptomatic group. When comparing symptomatic and asymptomatic patients, there was no statistically significant difference in thermal thresholds.

Batista *et al*[43] studied 60 adult subjects (30 young healthy individuals without a history of diabetes, and 26 individuals with adult onset diabetes and four with juvenile onset). Thermal sensitivity testing was performed with custom devices fabricated from materials with different thermal conduction capacities (copper, steel, glass, and plastic). There was a strong relationship found between cold perception and stimulation with the copper probe in dermatomes of the radial nerve of the upper limb and the superficial peroneal dermatome of the lower limb. The study concluded that thermal sensitivity to copper and cold stimulation might be more discriminative and have a higher threshold than sensitivity to the Semmes-Weinstein monofilament.

Levy *et al*[44] compared the method of limits or a forced-choice method for testing TPT, cooling and heat pain thresholds in 367 diabetic patients, 128 with symptomatic neuropathy. FC thermal thresholds increase with age in normal subjects, but not to a clinically significant degree. In diabetics FC warm threshold increased by 0.8^0C/decade, ML by 0.1^0C/decade. The prevalence of abnormal thresholds was found to be similar for both methods (28-32%). Only 15-18% of patients had abnormal results in both tests.

Bertelsmann *et al*[45] investigated thermal cutaneous sensation (thermal discrimination thresholds) of the hand and the foot in 36 normal subjects and in 20 patients with diabetic neuropathy. In patients with diabetic neuropathy the increased thresholds for the foot could be correlated with length-dependent degeneration of small nerve fibres.

Guy *et al*[46] undertook sensory evaluation of thermal sensitivity in four groups of patients with diabetic neuropathy: 22 with neuropathic ulcers and/or Charcot joints (groups 1 and 2); 15 patients with painful neuropathy (group 4), 10 patients with autonomic neuropathy alone (group 3) and found that thermal testing was able to detect abnormalities in all 4 groups. Comparison of thermal sensitivity (a small fibre modality) with vibration perception threshold (a large fibre modality) showed that thermal sensitivity was sometimes selectively affected, which suggested that the small fibres are more vulnerable in diabetes.

Cooling detection thresholds

Dyck *et al*[47] evaluated neuropathic symptoms [neuropathy symptom score (NSS) and neuropathy scale of neuropathy symptom profile (NNSP)], deficits [neurologic disability score (NDS) and vibratory (VDT) and cooling (CDT) detection thresholds], or nerve dysfunction [nerve conduction (NC)] in 180 diabetics, and found that NC was abnormal in 69%, NSS in 54%, NDS in 48%, NNSP in 47%, VDT in 44%, and CDT in 35%.

Heat pain thresholds

Hilz *et al*[48] determined the parameters that predict alterations in warm, cold and heat pain threshold using a "Marstock" Thermo-stimulator in 26 diabetics and 32 healthy subjects. While heat pain determinations were not useful, determination of cold perception, at a moderate rate of temperature change, proved to be the most reliable indicator of small fiber lesions. Cold thresholds as well as their intra individual ranges were most often impaired.

Interventions

Curcumin

Sharma *et al*[49] explored the antinociceptive effect of curcumin and its effect on tumour necrosis factor-alpha (TNF-alpha) and nitric oxide (NO) release in streptozotocin induced diabetic mice and found that 4 weeks treatment with curcumin attenuated thermal hyperalgesia and the hot-plate latencies. Their study results indicated an antinociceptive activity of curcumin possibly through its inhibitory action on NO and TNF-alpha release.

Lycopene

Kuhad *et al*[50] explored the antinociceptive effect of lycopene and its effect on tumour necrosis factor-alpha (TNF-alpha) and nitric oxide (NO) release in streptozotocin induced diabetic mice which were tested in the tail immersion and hot-plate assays. Lycopene treatment significantly attenuated thermal hyperalgesia and the hot-plate latencies.

Quercetin

Anjaneyulu and Chopra[51] explored the antinociceptive effect of a bioflavonoid, quercetin, both in control and streptozotocin (STZ)-induced diabetic mice and found that Quercetin (100 but not 50 mg/kg p.o.) produced a marked increase in tail-flick latencies of thermal (warmth) hyperalgesia in both diabetic and nondiabetic mice.

Resveratrol

Sharma *et al*[52] explored the antinociceptive effect of resveratrol on diabetic neuropathic pain in DPN rats and found that daily treatment with resveratrol for 4 weeks starting from the 4th week of STZ injection significantly attenuated thermal hyperalgesia.

Tapentadol

Christoph *et al*[53] studied effects of Tapentadol (a novel analgesic with two modes of action, mu-opioid receptor (MOR) agonism and noradrenaline (NA) reuptake inhibition) on thermal hyperalgesia in DPN mice and found that Tapentadol was more potent than morphine against heat hyperalgesia in a dose-dependent manner.

Transplantation of bone marrow-derived mononuclear cells

Naruse *et al*[54] investigated whether transplantation of freshly isolated bone marrow-derived mononuclear cells (BM-MNCs) alleviates neuropathic pain in the early stage of streptozotocin-induced diabetic rats, and found that BM-MNC transplantation significantly ameliorated mechanical hyperalgesia and cold allodynia.

Trolox

Sharma and Sayyed[55] targeted oxidative stress in DPN using trolox, an anti-oxidant, in streptozotocin-induced diabetic neuropathy in

rats and found two weeks treatment with trolox started on completion of the 6th week of diabetes significantly improved MNCV, NBF and inhibited thermal hyperalgesia.

Discussion

The objective of this study was to explore and synthesize the existing evidence for thermal perception and its testing and treatment methods in DPN from a bench-to-bedside perspective. The existing evidence although limited, provide a fairly sufficient information on role of thermal perception and its evaluation of small-fiber dysfunction in DPN which presented either positively or negatively and the therapeutic role of a myriad of management methods for ameliorating thermal hyperalgesia or allodynia.

Reliability of thermal quantitative sensory testing was variable, with the reliability of cold and warm detection thresholds ranged from poor to excellent, while heat and cold pain thresholds ranged from fair to excellent.[56] Thermal perception threshold and thermal pain threshold testing are influenced by inter-trial interval and the order of testing.[57] It is also essential to evaluate pain ratings during threshold testing in order to standardize the interpretation of QST.[58]

The use of thermal QST in people with pain raises questions proposed by Granot *et al*:[59] "(a) Are pain scores for short-term repeated phasic stimuli consistent? (b) Does an exposure to tonic heat pain stimulus cause sensitization and change the scores for subsequent phasic stimuli? and (c) Are pain scores for phasic and tonic heat pain correlated? Which were answered respectively as follows: (i) phasic pain scores assessments at 30' and 60' after baseline is consistent; (ii) tonic heat pain, despite relatively high VAS scores, does not cause a change in the scoring of subsequent phasic stimuli; and (iii) phasic and tonic pain scores correlate with each other."

Factors such as age (Lin *et al*, 2005),[60] site of testing, temperature of part,[61] skin temperature distribution,[62] stimulus (type, characteristics, quantity, presentation, testing format, and environment) but also the response (form and analysis),[63] types of instruments,[64] cutaneous mechanoreceptors,[65] determination paradigm and reference temperature[66] influence the accuracy of testing and these should be invariably kept in mind by the practicing clinician.

There were different methods of recording-method of limits[67] which can reliably detect c- and a-delta fiber-mediated thermal perception[68] which deserve comparison in people with DPN. Olney[69] provided recommendations for clinical trials on polyneuropathy using QST as outcome measures that cooling and warming detection thresholds have good sensitivity for small myelinated sensory fibers.

Recent developments such as computer-assisted sensory examination of thermal thresholds were reported to be accurate, convenient and inexpensive, where the clinical data could easily be utilized as a scientific data.[70] Such methods would enable better knowledge-practice translation of evidence-informed scientific developments.

Future assessment studies should compare the measurement properties of types and methods of thermal perception and thermal pain threshold testing for enhancing their evidence-informed use in assessment of people with DPN. Future intervention studies should study the effects of interventions on small-fiber dysfunction in DPN through thermal sensory testing methods.

Conclusion

Thermoregulation and thermal sensory perception were altered in DPN, which was evidently demonstrated as changes in temperature, responses to immersion, heat evoked potentials, thermal perception thresholds, and thermal pain thresholds during assessment, and was positively reflecting therapeutic effects, efficacy and effectiveness of variety of interventions.

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Original Article

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Spectrum of Gastrointestinal Polyps in Children: Does Eosinophilic Infiltration in Juvenile Polyps Have Any Significance?

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Abstract

Context: Gastrointestinal polyps are common in children with juvenile polyps being the most common type, accounting for 90% of cases.[1] The reported incidence of juvenile polyposis syndrome is between 1 in 100,000-1 in 160,000.[2] Present study reviews histopathology, distribution and clinical manifestations of gastrointestinal polyps in children and significance of mucosal eosinophilia in Juvenile polyps. A comprehensive knowledge of these disorders is necessary for correct treatment and follow up.

Aims: To study histology and distribution of intestinal polyps and to analyze significance of stromal eosinophilia in the pathogenesis of Juvenile polyps.

Settings and Design: Three year retrospective and two year prospective study between May 2007 and April 2012.

Methods and Materials: Forty two cases of gastrointestinal polyps in children were studied. Polyp size, number and location were noted. Association between stromal eosinophilia and age/size in case of juvenile polyps was studied.

Statistical analysis: Chi square test (PSPP software)

Results: There were thirty four solitary juvenile polyps, two multiple juvenile polyposis cases, three inflammatory polyps and three Peutz Jeghers polyps. Most common site was rectum and mean age was 6.7 years. Eosinophilic infiltration showed positive correlation with size and inverse correlation with age in juvenile polyps.

Conclusions: Majority of polyps in children are solitary juvenile polyps. Presence of significant eosinophilic infiltration of polyps may suggest a role of allergy in etiopathogenesis of juvenile polyps.

Keywords: Eosinophilic infiltration; Gastrointestinal polyps; Pediatric polyps.

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Introduction

The word polyp comes from the Greek word "polypus" meaning 'many footed'. A polyp is

any excrescence or growth protruding above a mucous membrane.[3] Majority of polyps in pediatric age are solitary juvenile polyps.[1] Their etiology is still unknown. Roma Gianikou *et al* have reported increased incidence of stromal eosinophilia in cases of juvenile polyps.[4] Taking in view the presence of eosinophils in a number of cases of juvenile polyps, we have endeavored to study the possible role of eosinophilic infiltration in the etiopathogenesis of these polyps. We have also studied other types of polypoidal lesions in pediatric age.

Materials and Methods

This was a three year retrospective and two year prospective study conducted between May 2007-April 2012. Forty two cases of gastrointestinal polyps in children were studied. Both polypectomy and bowel resection specimens were studied. Demographic data, mode of presentation, polyp size, number and location were noted. Sections were routinely processed and stained with Hematoxylin and Eosin.

Polyps were classified according to their size into the following categories: less than one cm, between one and two cm and above two cm. Significant eosinophilic infiltration in the lamina propria of polyp was defined as the presence of more than twenty eosinophils/high power field. Statistical analysis was carried out using the chi square test(PSPP software).

Results

Of the forty two cases studied, twenty three (54.76%) were boys and nineteen (45.24%) were girls. The age range was between two to twelve years with a mean age of 6.7 years. The mode of presentation was painless, intermittent rectal bleeding and mass per rectum in case of rectal polyps. The more proximally located polyps presented with abdominal pain, chronic rectal bleeding and anemia. Two cases presented with intussusception causing intestinal obstruction.

Thirty three cases had rectal polyps, four cases had colonic polyps, three cases had jejunal polyps and two cases had ileal polyps.

The polyps were also classified based on their histology. (Table 1)

There were thirty four (80.9%) cases of solitary juvenile polyps. Grossly, they were polypoidal, grey white masses ranging in size from 0.5 to 1.5 cm. Histology revealed many cystically dilated glands in an inflamed and edematous lamina propria containing inflammatory infiltrate composed of neutrophils, lymphocytes, eosinophils, plasma cells and histiocytes. (Figure 1)

There were two (4.8%) cases of multiple juvenile polyposis. In our study, the number of polyps ranged from ten to fifteen and were distributed throughout the colon. (Figure 2) Histological features were similar to solitary juvenile polyps.

There were three (7.1%) cases of Peutz Jeghers polyps. The polyps were located in jejunum and ileum and the number ranged between three and five. They were cauliflower like and pedunculated. Histology revealed a polyp containing smooth muscle in an arborizing arrangement covered by a mucosal lining.

There were three (7.1%) cases of inflammatory polyp. Histology revealed extensive inflammatory infiltrate and granulation tissue.

Table 1: Polyps classified according to histology

➢ Types of polyps	Solitary juvenile polyps	Juvenile polyposis coli	Peutz Jeghers polyps	Inflammatory polyps
Eosinophilic infiltration(>20/HPF)	30	0	0	0
Eosinophilic infiltration(<20/HPF)	4	2	3	3

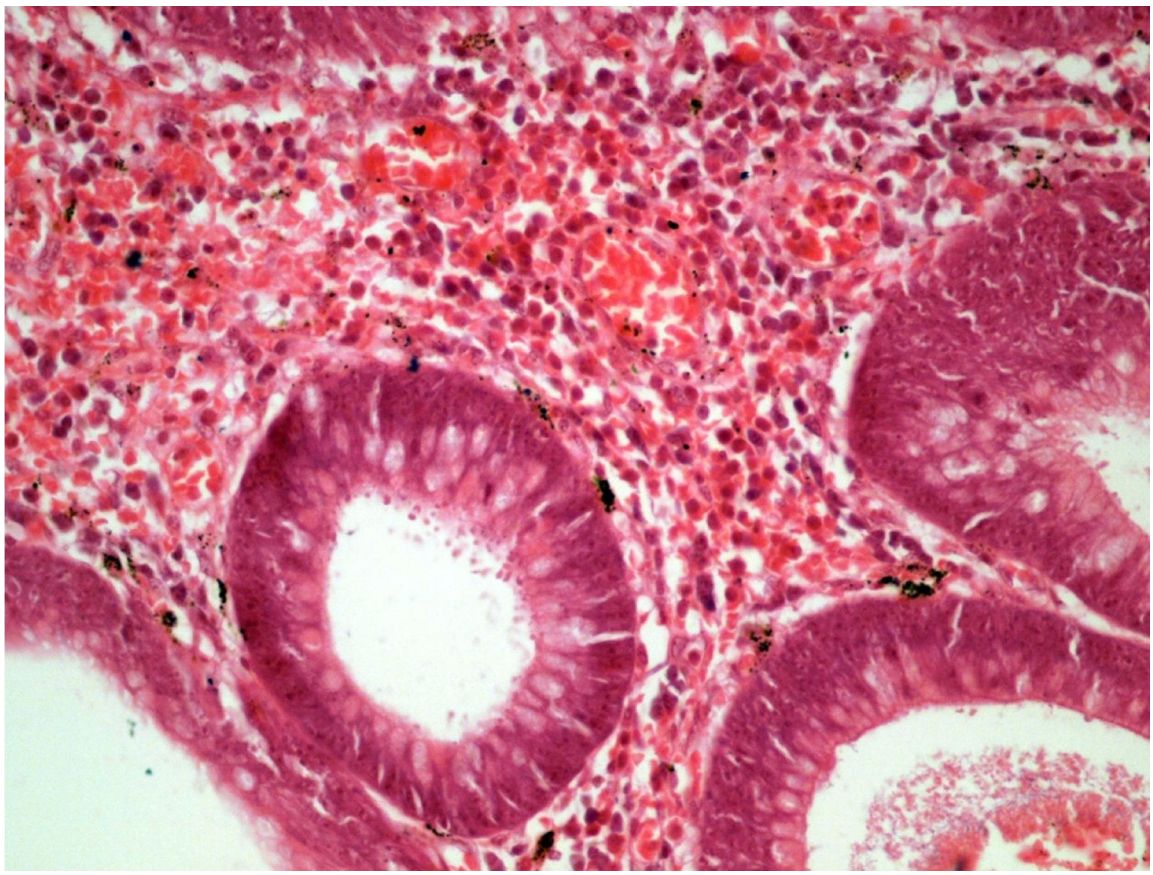
Table 2: Correlation of eosinophilic infiltration with size of juvenile polyps

➢ Size	<1 cm	1-2 cm	>2 cm	Total
Eosinophilic infiltration(>20/HPF)	7	19	4	30
Eosinophilic infiltration(<20/HPF)	5	1	0	6
Total	12	20	4	36

Table 3: Correlation of eosinophilic infiltration with age

➢ Age groups	2-4 years	4-6 years	6-8 years	8-10 years	10-12 years	Total
Eosinophilic infiltration(>20/HPF)	6	8	8	6	2	30
Eosinophilic infiltration(<20/HPF)	0	0	1	2	3	6
Total	6	8	9	8	5	36

Figure 1: Photomicrograph of juvenile polyp showing cystically dilated glands and dense infiltration with lymphocytes, eosinophils and histiocytes. H&E40X

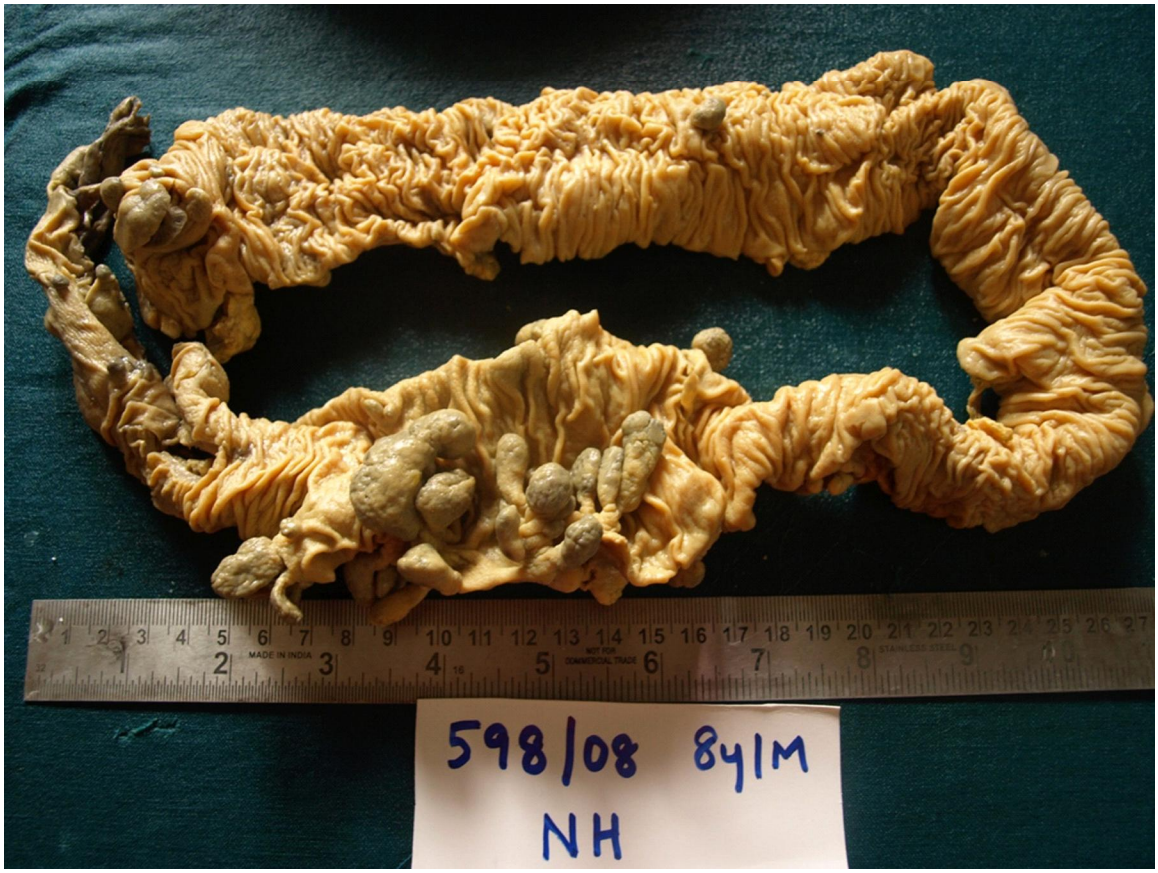


Of the thirty cases of juvenile polyps (thirty four solitary juvenile and two juvenile polyposis), thirty cases had significant eosinophilic infiltration in the polyps. Multiple juvenile polyposis cases did not show eosinophilic infiltration. None of the Peutz Jeghers and inflammatory polyps showed significant eosinophilic infiltration.

Thirty six children aged between two to twelve with juvenile polyps were studied for any relationship between size of the juvenile polyp and eosinophilic index (Table 2). Correlation between age of the patient and eosinophilic index was also studied (Table 3).

The results showed an inverse correlation

Figure 2: Gross photograph of Juvenile polyposis coli showing colon with multiple polyps



between increasing age and eosinophilic index with a Pearson's chi square value of 10.16 and a p-value of 0.04.

The test also showed a positive relationship between size and eosinophilic index with chi square value of 8.16 and p-value of 0.02.

Discussion

Gastrointestinal polyps are common in children and may pose a diagnostic challenge in some cases. Although demonstration of germ line mutation can confirm the diagnosis in some of the familial polyposis syndromes, it may not be possible in all cases. Hence the pathologist's accurate description of polyp assumes a critical role. This may have significant diagnostic implications both for the patient and his relatives due to the associated risk of malignancy in some of the polyposis syndromes.

The majority of polyps in pediatric age group are solitary juvenile polyps or retention polyps accounting for ninety percent of cases.[1] Estimates reveal that one to two percent of children have one or more juvenile polyps in the age groups of two to ten years.[2] They usually present with bleeding per rectum. Solitary Juvenile polyps have essentially no malignant potential. However when juvenile polyps are multiple, risk of cancer is present.[5]

Juvenile polyposis syndrome is an autosomal dominant syndrome characterised by mutations in *SMAD4* and *BMPR1A* genes.[5] It can be defined by any one of the following criteria: five or more juvenile polyps of the colon and rectum, juvenile polyps throughout the gastrointestinal tract, or any number of juvenile polyps in the gastrointestinal tract with a family history of juvenile polyps.[2] JPS is associated with enhanced risk for development of colonic, gastric, intestinal, and pancreatic carcinoma.[5]

Peutz-Jeghers syndrome (PJS) is an autosomal dominant hamartomatous polyposis syndrome associated with mucocutaneous hyperpigmentation. Its prevalence is 1 per

200,000 cases.[5] The diagnosis of PJS is clinically established by the presence of histologically confirmed hamartomatous polyps with any two of the following criteria: a positive family history of PJS; mucocutaneous pigmentation and presence of small-bowel polyps.[5] The mucocutaneous pigmentation is found most commonly around the mouth, nose, lips, buccal mucosa, hands, feet, perianal and genital regions. The polyps in PJS may be found in the stomach, small intestine, or colon being most prominent in the small intestine. The polyps have a unique histology, composed of proliferating and crisscrossing smooth muscle bundles, which give the appearance of a tree and its branches, hence the term 'arborisation'.[5]

Present study is consistent with studies conducted so far in many aspects that most common polyps in children are benign juvenile polyps. They are more common in boys than in girls and the most common site is rectum. They usually present with painless rectal bleeding and are more common in first decade of life as is the case in the present study.

Our study results are corroborated by Salma Fettahoglu *et al*.[6] The number of juvenile polyps carries significance because presence of more than five polyps indicates the presence of juvenile polyposis. Juvenile polyposis syndromes harbor a risk of increased malignancy having a thirty nine percent cumulative life-time risk of colorectal cancer.[2]

Little is known about the etiology of juvenile polyps. Lipper *et al* have proposed that disturbed cell surface renewal leads to erosion of mucosal surfaces leading to inflammation and granulation tissue formation.[7] Iwamoto *et al* have reported accumulation of beta catenin in epithelial cells of juvenile polyps.[8] Roma Gianikou *et al* have reported increased incidence of stromal eosinophilia in cases of juvenile polyps.[4] Alexander *et al* proposed allergy as a possible factor in etiopathogenesis of polyps.[9] In our study we have observed a positive relationship between size and eosinophilic index and an inverse correlation between increasing age and eosinophilic index in case of juvenile polyps. So we could also propose the role of eosinophilia and in turn allergy as a possible etiopathogenic factor. Eosinophils are a source of many cytokines which may contribute to evolution of polyp supporting an inflammatory etiology. Very few studies have been conducted so far studying the association between juvenile polyps and allergic disorders. Additional studies with detailed clinical work up for allergic disorders in such cases would shed further light upon the etiopathogenesis of juvenile polyps.

Conclusion

In conclusion, solitary juvenile polyps are the most common polyps observed in pediatric age group. In our study, we have observed a positive correlation between eosinophilic infiltration and size of the polyp and an inverse correlation with age. In view of these findings, we propose an allergic etiology for juvenile polyps.

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Case Report

Indian Journal of Pathology: Research and Practice

Role of Fine Needle Aspiration Cytology in the Evaluation of Cysticercosis - Subcutaneous and Intramuscular

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Abstract

Objective: To study the role of FNAC in the diagnosis of cysticercosis. **Materials and Methods:** Thirty patients with subcutaneous and intramuscular nodules having a differential diagnosis of tuberculous lymphadenopathy, reactive lymphadenitis, lipoma, neurofibroma and cysticercosis were included in the present study. **Results:** FNAC proved to be the definitive diagnosis in 13 cases where fragments of parasite bladder wall were seen. Histopathology confirmed the diagnosis. In the rest 17 cases, no fragments were observed in the FNAC smears and parasitic inflammation was suggested on the basis of other cytomorphological findings. Follow-up biopsy confirmed the diagnosis of cysticercosis. **Conclusions:** FNAC in cysticercosis is an easy , reliable ,cost effective non invasive outpatient procedure . The cytological diagnosis is conclusive in the cases where fragments of actual parasite are identified in the smears. However, in other cases, presence of a typical granular dirty background, eosinophils or/and histiocytes ,giant cells etc. Give an insight to the pathologist to consider this possibility. Definitive evidence on cytology obviates the need for histopathology.

Keywords: Cysticercosis; Fine needle aspiration cytology; Parasite.

Introduction

Cysticercosis is a potentially fatal parasitic disease relatively common in developing countries of Central and South America, Asia, and Africa, especially in those areas where humans and animals live in close contact, and in those regions where inspection of meat is not strict. In humans, cysticerci are most commonly located within the central nervous system (CNS), where they produce a pleomorphic clinical disorder known as neurocysticercosis. It may also primarily be located in a variety of tissues, including muscle, heart, eyes, and skin.[1]

Man occasionally serving as the larval host of *Taenia solium* becomes infected either by drinking contaminated water or by eating uncooked vegetables infected with eggs.[2] The preoperative diagnosis of cysticercosis can be made by computed tomography (CT) scan and magnetic resonance imaging (MRI)] and serological tests like complement fixation test, hemagglutination, radioimmunoassay and enzyme linked immunosorbent assay (ELISA).

Fine needle aspiration cytology (FNAC) is now available as a preoperative tool for the diagnosis of subcutaneous cysticercosis. The diagnosis is confirmed by the histopathological examination of the excised specimen.

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Materials and Methods

This study included 30 patients presenting with palpable subcutaneous and intramuscular nodules at different sites. FNAC was performed with 22-gauge needle and 20 ml BD syringe and smears made on glass slides.

May-Grünwald-Giemsa staining was done after air drying and fixing with methanol.

Subsequent excision biopsy was also evaluated.

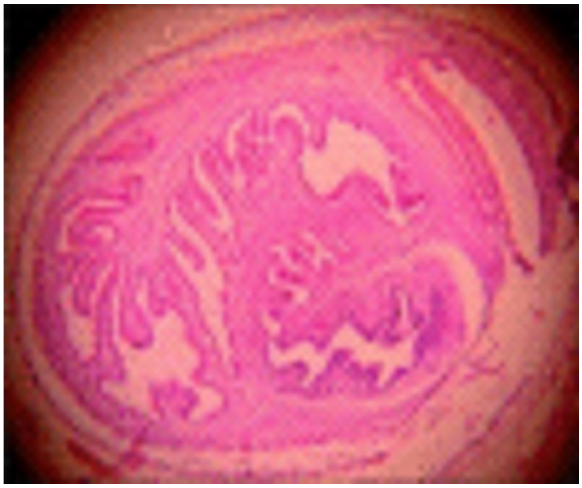
Results

The present study included 30 patients in the age group 2–65 years coming to the Cytology Department of Santosh Medical College, Ghaziabad. There was no obvious sex predilection in the present study wherein 13 subjects were females and 17 were males.

25 cases had solitary nodule while 5 cases presented with multiple nodules.

9 cases presented with neck nodules, 7 with abdominal lumps, 7 with nodules on extremities, 2 with swelling axilla, 2 with preauricular nodules, 2 with nodules on the back and one with forehead nodule.

Figure 2: Cysticercus larva enclosed in a thin fibrous cyst wall (H&Ex40X)

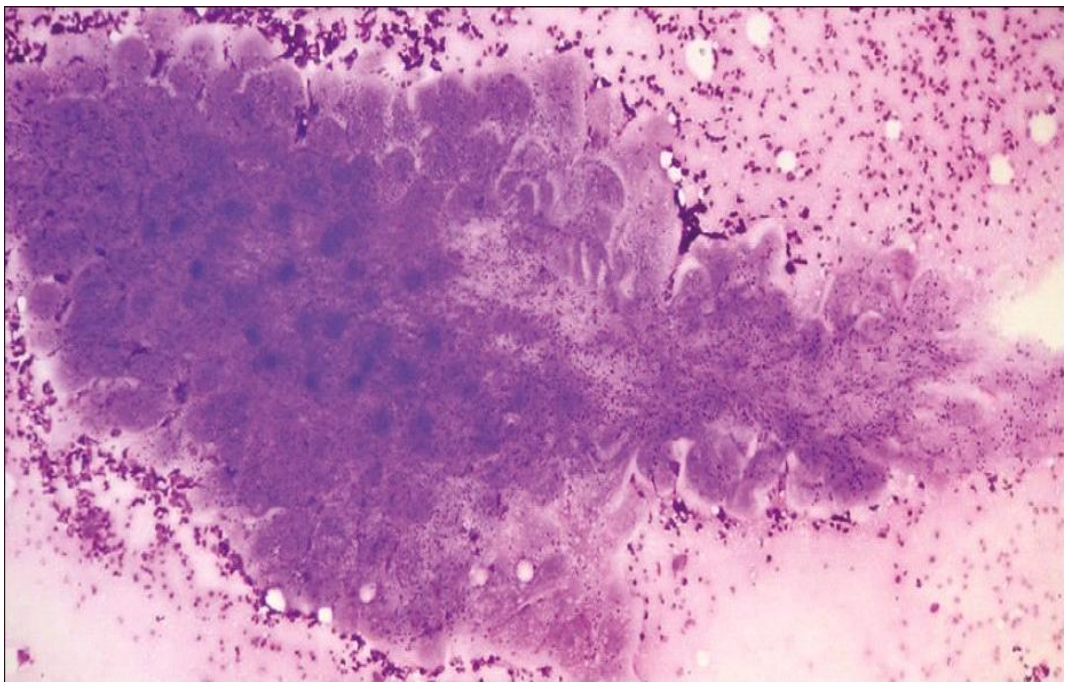


All the patients presented with painless slow growing nodule, soft to firm in consistency, and the provisional diagnoses were reactive lymphadenopathy, lipoma, neurofibroma, sebaceous cyst, tubercular lymphadenopathy and cysticercosis depending on the site.

In 27 cases, the aspirated material comprised of clear to dirty fluid while 3 cases yielded purulent fluid.

In 13 cases, on FNAC, smears showed

Figure 1: Cysticercus tegument and parenchyma (MGG×40X)



parasite wall, fragments and/or hooklets although the cytomorphology was not exactly the same in all cases. Follow-up biopsy confirmed the diagnosis. In the rest 17 cases, the cytological findings were very much suggestive of a parasitic cyst but no parasite could be seen. The smears showed a mixed inflammatory infiltrate comprising neutrophils, lymphocytes, eosinophils, histiocytes and giant cells (in varying proportions in different cases). In 3 of these 17 cases, well-formed epithelioid cell granulomas were also evident but no acid fast bacilli were seen on Ziehl Neelson staining. A cytological diagnosis of parasitic cyst was suggested and excision was advised. Follow-up biopsy confirmed the diagnosis of cysticercosis.

Discussion

Man is the definitive host for Taenia solium or tapeworm, a parasite found in the small intestine. Eating of undercooked and contaminated pork by man results in the larvae reaching the small intestine, where they develop into the adult stage of Taenia solium. The terminal segment of the parasite (proglottids) contains eggs and these are excreted in the feces. The feces, dispersed on the surface of the ground may be ingested by pigs, the intermediate host. The gastrointestinal secretions of the pig dissolve the eggs and liberate the embryos or enchospheres. These embryos then penetrate the intestinal mucosa and gain access to either the vascular or lymphatic circulation and are thus distributed to various tissues or organs, particularly skeletal muscles, subcutaneous tissue, eyes and the central nervous system. Here they develop into cysticercus cellulosae, the larval form of this parasite.[1,3]

Eating of undercooked and contaminated pork by man results in the larvae reaching the small intestine, where they develop into the adult stage of Taenia solium.

Parasitic fragments may comprise bluish, fibrillary structures, sometimes with honeycombing, calcospherules, tegument thrown into rounded wavy folds, scolex with hooklets, and hyaline membrane surrounding it.[4]

Fully developed cysticerci are opalescent, milky white cysts, elongated to oval and about 1 cm in diameter. The cyst contains fluid and a single invaginated scolex. The scolex has a rostellum, four suckers and 22–32 small hooklets. The cyst wall is multilayered, 100–200 mm thick and covered by microvilli. The outer, cuticular layer appears smooth and hyalinized and is frequently raised in projections. Beneath the tegument is a row of tegumental cells. The inner layer or parenchyma is loose and reticular, containing mesenchymal cells and calcerous corpuscles.[5] The calcareous corpuscles are a unique feature of cestode tissue. These spherical, noncellular masses occur in the parenchyma and are especially prominent in larval cestodes. The corpuscles take on a bluish purple color in hematoxylin and eosin (H and E).[6]

Cyticerci nodules in the skin are difficult to differentiate from benign mesenchymal tumors and lymphadenitis on clinical grounds alone.[7] The cytomorphological identification of larvae in FNAC smears by different workers has widened the diagnostic utility of FNAC in skin nodules.[2,7,8] Suspicion about a parasitic lesion starts with the presence of eosinophils, neutrophils, palisading histiocytes and giant cells in an aspirate from subcutaneous nodule. A careful search for parasitic fragments should be carried out in the presence of polymorphous inflammatory infiltrate composed predominantly of eosinophils and histiocytes.[4]

The diagnosis of cysticercus is made when fragments of larval cuticle and parenchyma are identified.

Viable cysticerci may not cause any inflammatory response. However, when they degenerate, there is an infiltration of inflammatory cells, associated with the development of foreign body granulomas. The viable cyst and the necrotic and calcified lesions all have distinctive cytomorphological patterns. The viable cyst yields clear fluid and shows fragments of bladder wall in a clear acellular background. Aspirates of necrotic lesions may contain fragments of bladder wall, including

calcareous corpuscles and detached single hooklets.[9]

FNAC in cysticercosis is a low-cost outpatient procedure. It is one of the tools for preoperative diagnosis and may even obviate the need for open biopsy.

The cytological diagnosis is conclusive in cases where actual parasite structure is identified in the smears. However, in other cases, the presence of a typical dirty background, eosinophils, histiocytes single or in pallisaded clusters or a foreign body granuloma, etc. are the features which should always alert the pathologist to this possibility.

Nonetheless, in still some cases of cysticercosis, none of these features may be present, and the inflammatory infiltrate may also be variable. Cysticercosis is more common than usually thought.

In all inflammatory/cystic/inflammatory cystic lesions, the possibility of cysticercosis should be kept in mind.

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Case Report

Indian Journal of Pathology: Research and Practice

Primitive Polar Spongioblastoma: A Rare Histopathological Entity

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Abstract

Primitive Polar spongioblastoma is a very rare histopathological entity characterized by bipolar tumor cells with palisading nuclei showing immunoreactivity for neuron-specific enolase. The entity was first described by Russell and Cairns in 1947. It is classified as a high grade glioma with a very poor prognostic outcome. However, similar histological profile is often seen in many neuroepithelial tumors, and this category was earlier excluded from the World Health Organization (WHO) classification raising the question of its existence as a tumour entity. Presently, it is included in WHO classification in the category of CNS tumour of uncertain origin. To our knowledge, only a few cases of Primitive polar spongioblastoma have been reported so far. The present case of a 65 yr old male clinically presenting with vomiting & altered sensorium. MRI findings were inconclusive suggesting a mass lesion in the temporal lobe & a presumptive diagnosis of tumoral bleed was given.

Keywords: Glioma; Neuroepithelial; Palisading; Spongioblstoma.

Introduction

Polar spongioblastoma was first described by Russell and Cairns in 1947. It is a high grade glioma characterised by the parallel palisading of spindle tumor cells without microvascular proliferation (MVP) and necrosis. Different views have been suggested regarding the existence of this rare entity as nuclear palisades can be found as local architectural features in many neuroepithelial tumors like ependymomas and neuroblastomas.

Case Presentation

A case of a 65 yr old male clinically presenting with frequent vomiting, altered sensorium & headache. CT scan findings were inconclusive. EEG was normal but MRI suggested a mass lesion in the temporal lobe,

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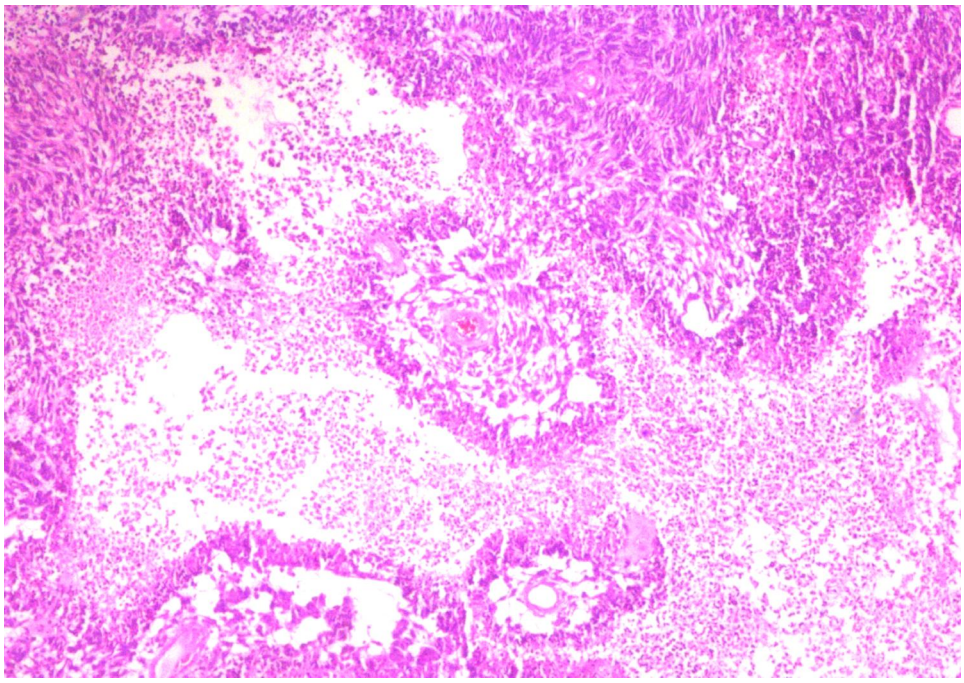
Figure 1: H & E -100X-Tumour Cells In Palisading Pattern



measuring 3x2x2.5 cm, a provisional report of tumoral bleed was given. Per-operatively, a highly vascular, non suckable tumour mass was seen and excisional biopsy was performed. Histopathological examination was done. Grossly, the tumour consisted of multiple greyish white soft tissue pieces. On microscopic examination, a highly malignant neoplasm composed of bipolar cells arranged in palisades of long columns was seen with intervening fibrillary zone in a linear arrangement (Figure 1, 2). Nuclei are hyperchromatic, round to oval. Mitotic activity is scant. IHC analysis revealed NSE positivity (Figure 3) & negative CK. The confirmed histopathological diagnosis of Primitive polar spongioblastoma was given.

Figure 2: H & E-400X-Columns Of Bipolar Cells With Intervening Fibrillar Zone

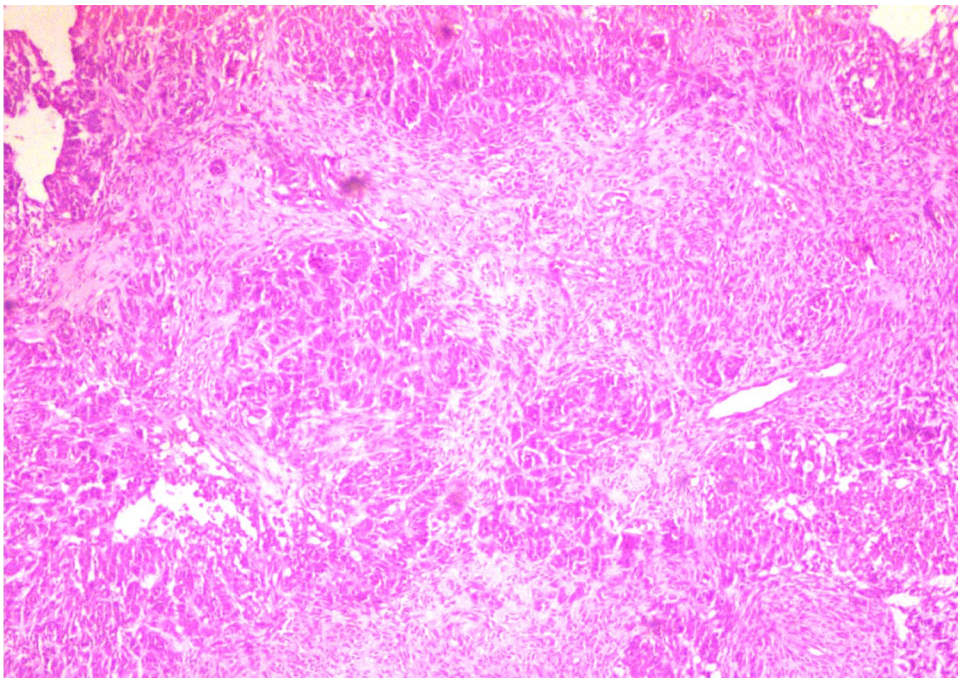
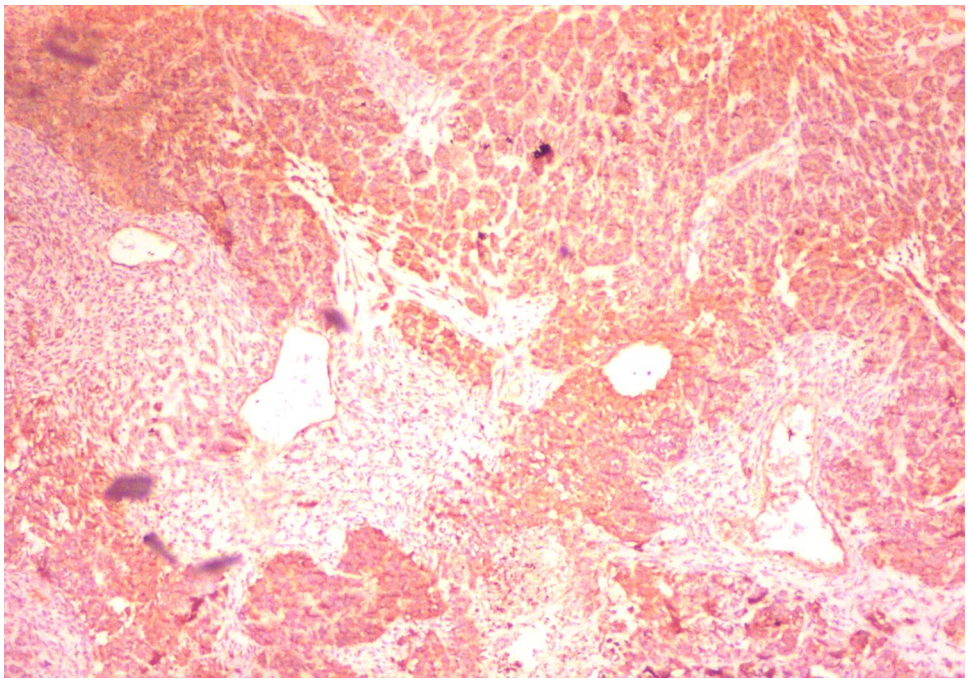


Figure 3: Tumour Cells Showing Nse Positivity- (X400)



Discussion

A study by Narita Y and Fukushima S[1] in 2012 in a 44 yr old adult who presented with a headache exhibited a tumor of the right frontal lobe on MRI. Histological diagnosis of the tumor obtained by gross total resection was high-grade glioma, which was composed of the parallel palisading of spindle tumor cells, final diagnosis of a high grade glioma with histological pattern of polar spongioblastoma was made. It was suggested that this tumor might not be suited to any of the neuroepithelial tumors in the current WHO classification. Contrary to these findings, in a study by Schiffer D[2] in 1993, The distribution of cells in a parallel fashion with palisades of nuclei is common in neuroepithelial tumors and thus polar spongioblastoma does not exist as a tumor entity as pilocytic astrocytomas, oligodendrogliomas, medulloblastomas, cerebellar astrocytomas, neuroblastoma also present with similar histological profile. Concordance to the earlier views was seen in a case report of a 14 months old baby by Langford[3] (1987) stating that the pallisading pattern in cerebral neuroblastoma mimicks juvenile polar spongioblastoma. Ultrastructural examination of this single case reveals cells that range from the embryonal neuroepithelial cell to neurons with synapse formation. The diagnostic pattern characteristic of the polar spongioblastoma may be found in tumors of neuronal origin, although most polar spongioblastomas having the typical pattern of palisading seem to belong to the astrocytic cell line. A study by G.H. Jansen *et al*[4] in 1990, revealed juvenile polar spongioblastoma as a distinct electron microscopic entity with ultrastructural features of developing neuronal elements. These findings are in contrast with the longheld view that the polar spongioblastoma is cytogenetically related to the embryonal radial glial cells as revealed in a study by Chandarevian *et al*[5] 1984. The most important leading view in this respect comes from the current WHO classification which includes primitive polar spongioblastoma in neuronal tumours of uncertain origin.[6] The rhythmic pattern of uni and bipolar cell arrays is exclusively represented and aggressive biological behavior makes it a distinct entity.[7] Studies have proved that presence of a such palisading pattern mimicking polar spongioblastoma in an otherwise well differentiated tumour like cerebellar astrocytoma should be treated with aggressive chemotherapy & radiotherapy.[8]

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Case Report

Indian Journal of Pathology: Research and Practice

Non Dentigerous Type Unicystic Ameloblastoma in Canine-Premolar: Rare among Common: Case Report

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Abstract

Ameloblasoma comprises 1-2 % of all cysts and tumors occurring in jaw. Unicystic ameloblastoma is a less aggressive variant of ameloblastoma mainly seen in younger age group with impacted tooth in mandibular ramus area. In present case young male patient developed asympotomatic swelling with no impacted tooth in the region of canine – premolar with histological features of mural and intraluminal proliferation pattern of unicystic ameloblastoma.

Keyword: Ameloblastoma; Odontogenic; Mural.

Introduction

The unicystic ameloblastoma, a variant of ameloblastoma developing within the lining, lumen or wall of a cyst as well as an invasive ameloblastoma that has a single cystic space rather than multi cystic spaces.[1]

It shows ameloblastomatous epithelium lining part of the cyst cavity, with or without luminal and/or mural tumor proliferation.[2] They are seen in a younger age-group than solid tumors.[3] It is considered as less aggressive variant.[4]

The present case intraluminal and mural proliferation pattern is seen in canine-premolar region with no impacted tooth, which has been seen in very few reported cases.

Case Report

22 years old male patient had complaint of swelling in the lower left back jaw since 1 month with gradual progression & mild pain. On extra oral examination a diffuse swelling of approximately 2 cm in lower anterior region of left side of mandible (Fig 1), firm in consistency, non tender with no discharge. Intra-orally, swelling was in relation to 33, 34 and 35 region. Surface appeared smooth and well defined margins with no color change. A clinical diagnosis of odontogenic cyst and

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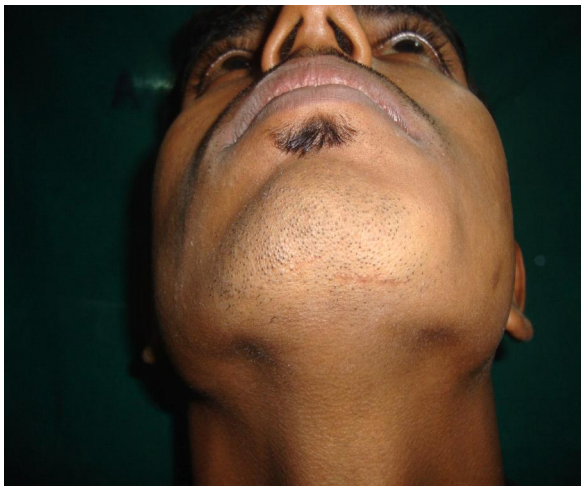
Fig 1: Diffuse swelling of 2 cm (approx) in lower anterior region of left side of mandible



benign odontogenic tumor was considered.

Orthopantomograph(OPG) and occlusal view (Fig 3 & 4) revealed well defined radiolucent lesion in relation to 33, 34 and 35 with lingual extension of the lesion. Aspiration suggested a cystic lesion. Excision of the lesion under general anesthesia was done. Gross examination of the excised specimen revealed cystic lining with nodular growth within lumen.

Histopathological examination show fibrous cyst wall with a lining that consists of ameloblastic epithelium. Epithelium shows basal layer of columnar cells with hyperchromatic nuclei that show reverse of polarity & basilar cytoplasmic vacuolization. Overlying epithelium in some areas resemble

Fig 2: Intraoral findings show small elevation with no color change

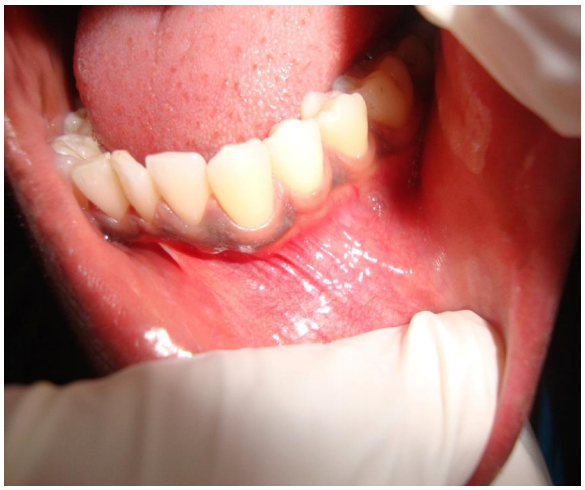


Fig 3: OPG shows unilocular cystic space below 33, 34 & 34

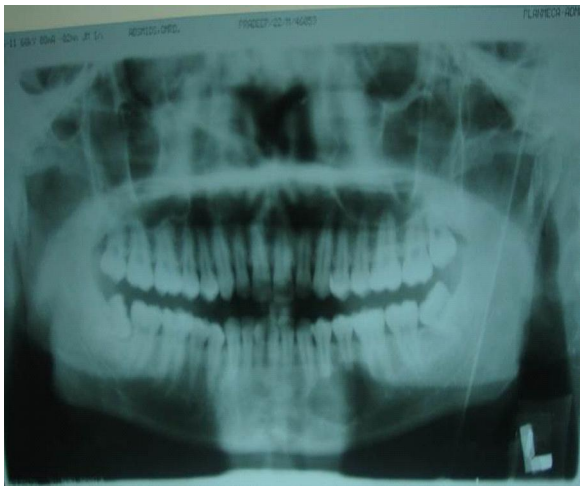


Fig 4: Occlusal view shows radiolucency extended to lingual side

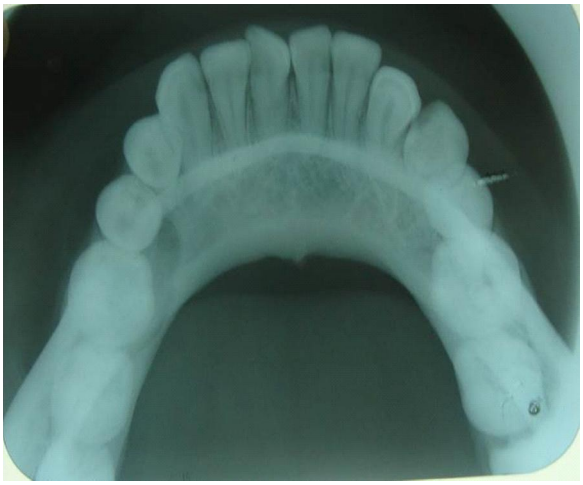


Fig 5: Gross specimen

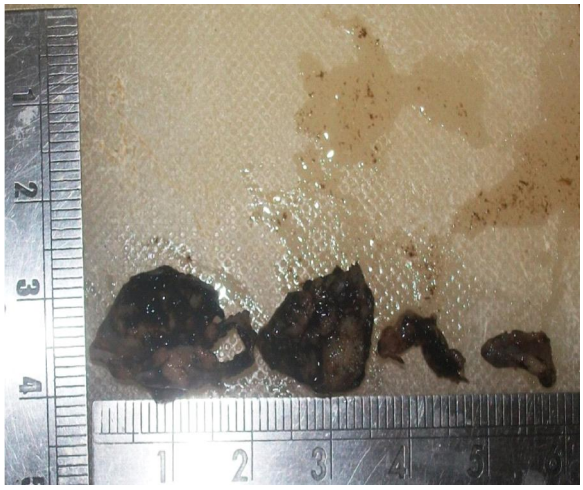


Fig 6: Shows mural proliferation

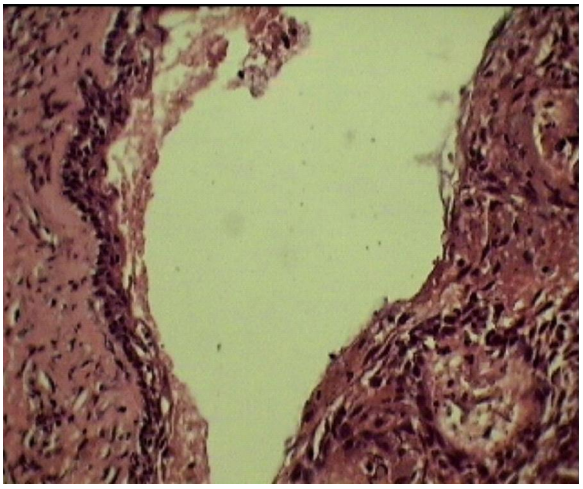


Fig 7: Shows intraluminal proliferation

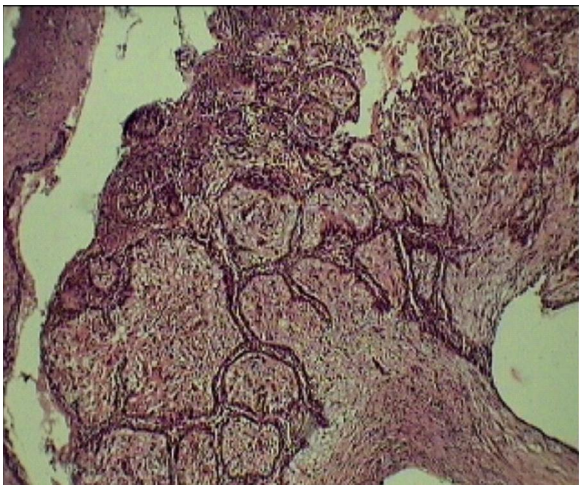
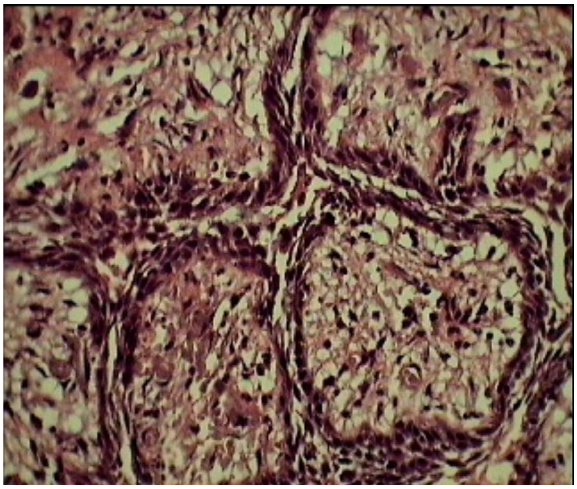


Fig 8: Shows Plexiform pattern with central stellate reticulum



stellate reticulum and shows mural and intraluminal proliferation in the plexiform pattern. Few areas showed subepithelial hyalinization. A diagnosis of unicystic ameloblastoma with mural and intraluminal proliferation was made.

Discussion

Unicystc ameloblastoma (UCA) is a rare type of ameloblastoma, accounting for about 6% of ameloblastomas and diagnosed histo-pathologically as unicystic ameloblastoma, if a single cystic sac lined by odontogenic (ameloblastomatous) epithelium, often seen only in focal areas.[5]

The neoplasm originates within the mandible or maxilla from epithelium that is involved in the formation of teeth. Potential epithelial sources include enamel organ, odontogenic rests (cell rest of Malassez, cell rest of Serre) reduced enamel epithelium and epithelial lining of odontogenic cyst especially dentigerous cyst.[6]

Mandibular 3rd molar is mostly associated with impacted tooth in unicystic ameloblastoma (dentigerous type),[3] but a few cases are not associated with impacted teeth which are called non dentigerous variant. According to Konouchi H *et al*, mean age of non-impacted tooth related cystic ameloblastoma was 35 years in comparison to 16.5 years for the impacted tooth related variant.[7]

Leider *et al* proposed three pathologic mechanisms for evolution of unicystic ameloblastoma.[8]

a. The reduced enamel epithelium associated with a developing tooth undergoes ameloblastic transformation with subsequent cystic development.
b. Ameloblastomas arise in dentigerous or other types of odontogenic cysts in which the neoplastic ameloblastic epithelium is preceded temporarily by a non-neoplastic stratified squamous epithelial lining.
c. A solid ameloblastoma undergoes cystic

degeneration of ameloblastic islands with subsequent fusion of multiple micro cysts and develops into a unicystic lesion.

Ackermann classified this entity into the following three histologic groups:

Group I: Luminal UCA (tumor confined to the luminalsurface of the cyst)

Group II: Intraluminal/plexiform UCA (nodular proliferationinto the lumen without Infiltration of tumor cells into the connective tissue wall)

Group III: Mural UCA (invasive islands of ameloblastomatous epithelium in the connective tissue wall not involving the entire epithelium).

Another histologic subgrouping by Philipsen and Reichart[9] has also been described:

Subgroup 1: Luminal UCA

Subgroup 1.2: Luminal and intraluminal

Subgroup 1.2.3: Luminal, intraluminal and intramural

Subgroup 1.3: Luminal and intramural

UCA should be differentiated from other cysts because the former has a higher rate of recurrence than the latter.[5] Dentigerous cysts, odontogenic keratocyst, residual cysts, adenomatoid odontogenic tumour, giant cell lesions and sometimes solid ameloblastoma can be considered as differential diagnoses for a unilocular lesion with or without a 'dentigerous' relationship occurring within the jaws. However, keratocyst seldom shows cortical expansion, residual cysts are associated with missing teeth that have been extracted, adenomatoid odontogenic tumour has a predilection for anterior maxilla, central giant cell granuloma often arises anterior to first mandibular molar and solid ameloblastoma is seen less commonly in patients less than 30 years of age.[10]

Dense inflammatory infiltrates may induce hyperplastic epithelium and also cause intercellular oedema within cystic epithelium lining which appeared to be stellate reticulum and mimic ameloblastic proliferation.[11] In view of the reported ameloblastic potential of dentigerous cyst,[12] it is thus important to recognise true ameloblastomatous epithelium from ameloblastomatomatous-like epithelium. [13] Hence careful examination is must in radicular and dentigerous cyst.

The mural variety is seen to be more often associated with the 'non-dentigerous'type of these lesions, while the intraluminal proliferations are more than twice as frequent in UCAs of the 'dentigerous' type.[7] However in our case we observed both type of proliferation (mural and intraluminal) which make it a finding least documented.

Treatment is usually based on histology of unicystic ameloblastoma, if intraluminal then enucleation is sufficed but, if mural proliferation of ameloblastic epithelium then bony resection is mandatory. It is generally removed as dentigerous cyst without preoperative biopsy and Isacsson and associates considered biopsies of cystic lesion not to be recommended; all of the tissue must be included.

Conclusion

Our case showed proliferation of both mural and intraluminal which make it a finding least documented. We suggest that checking content of the lesion before doing removal of lesion whether cystic or solid; if possible CT scan and MRI are useful to know the extent of the lesion to prevent injury to neurovascular lesion.

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Letter to Editor

Indian Journal of Pathology: Research and Practice

Pathogenetic, Diagnostic, Therapeutic and Prognostic Role of Age in Diabetic Peripheral Neuropathy

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Abstract

This letter to editor was directed to explore the underlying evidence behind the pathogenetic, diagnostic, therapeutic and prognostic role of age in diabetic peripheral neuropathy (DPN) in order to establish an inter-relationship between physiology and pathology in the pathophysiology of DPN in its symptoms, signs, clinical presentation and impact on individual's life.

Keywords: Age; Ageing; Older people; Geriatric neurology, Elderly.

Pathogenetically, Valensi *et al*[1] assessed peripheral neuropathy in 135 diabetic patients (28 insulin-dependent diabetes mellitus (IDDM), 85 non-insulin-dependent diabetes mellitus (NIDDM), and 22 insulin-treated NIDDM patients) to determine the risk factors for neuropathy and microangiopathy. The clinical neurological stage was found to correlate with age and in women, nine electrophysiological parameters were more abnormal and correlated with age which demonstrated that age to have an effect on peripheral nerve function in DPN.

Diagnostically, Albers et al[2] evaluated nerve conduction measures of 429 patients from a multicenter diabetic neuropathy study and found that patients with type II diabetes were older than type I patients (54.5 versus 39.1 years). Age was found to be confounding the effects of gender and diabetes type upon nerve conduction measures, with similar effects as that of gender for type-2 DM but not for type-1 DM.

Armstrong *et al*[3] generated age-related reference values from 120 healthy volunteers and found that vibration perception thresholds (VPT) deteriorated significantly with age; expiratory inspiratory (E:I) ratio had a variable relationship with age for patients which appeared to be located below the 5th percentile of normal data. Higher age was found in patients with neuropathy than for those without neuropathy[4] and old age was demonstrated to be a risk factor for carpal tunnel syndrome in DPN by Comi *et al*.[5] Age above 40-years in people with DPN was also associated with presence of cholesterol gallbladder stone and had undergone

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operation for cholelithiasis.[6]

Prognostically, the role of age as a confounding factor was realized and thoughtfully implemented in many case-control studies using age-matched controls by Beylot *et al*[7] who studied the blood pressure response to standing and the heart rate variations during deep breathing (HRV) and standing; Mueller et al[8] who studied the gait characteristics, the plantar-flexor peak torques, and ankle range of motion; Resnick *et al*[9] who evaluated pressure sensation, vibration perception threshold, and electrophysiologic function of the peroneal nerve; Salsich *et al*[10] who assessed the relationships between plantar flexor (PF) muscle stiffness, strength (concentric peak torque), and dorsiflexion (DF) range of motion (ROM); and by Salsich *et al*[11] who measured passive ankle stiffness and dorsiflexion (DF) range of motion.

Surprisingly, the therapeutic role of ageing was not found in the existing knowledge base, and there is good scope for studying anti-ageing therapies and their role in DPN.

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