ORIGINAL ARTICLE

PREVALENCE OF DIGITAL CLUBBING IN HEALTH AND MALIGNANCY

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Background: Digital clubbing is the oldest known clinical sign. Though asymptomatic, it often predicts the presence of some chronic underlying pulmonary, cardiovascular, neoplastic, hepatobiliary, mediastinal, endocrine, or gastrointestinal disease. Not much information is available on its association with malignancy. Clubbing has been commonly associated with lung cancer, more often in non-small cell lung carcinoma. The objective of this study was to evaluate the prevalence of digital clubbing in patients with Oral Cancer (solid tumours). **Methods:** In this case controlled study, cancer patients attending the Oncology outpatient and their age matched healthy subjects were included. The cancer patients were grouped as Cases and the Control groups. All subjects were evaluated clinically and a uniform protocol for clubbing evaluation was applied. Their habits and any underlying coexisting disease were noted. **Results:** Over a period of 6 months, 72 subjects were recruited for the study, of which 36 were patients with diagnosed malignancy (Cases) and 36 were normal healthy subjects (Controls). Male:Female ratio in Cases was 3:1 v/s 2.2:1 in Controls. Seventy-two percent of the Cases were tobacco smokers compared to 27.8% in controls. In Cancer patients digital clubbing was positive in 26 (72.2%) compared to 8 (22.2%) in healthy Controls (p<0.001). In Cases, 84.6% having clubbing were smokers compared to 70% in controls with clubbing. **Conclusions:** Digital clubbing is strongly associated with serious underlying disease like cancer and its implications are still a clinical enigma. A significant association of clubbing and tobacco smoking is observed in head and neck cancer patients.

Keywords: Clubbing, digital clubbing, cancer, oral cancer, oropharyngeal cancer, hsCRP, CRP, head and neck cancer

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INTRODUCTION

Digital clubbing is an important clinical sign in medicine discussed since ancient times. The characteristic of digital clubbing is a focal bulbous enlargement of the distal phalanx and/or toes. Proliferation of connective tissue between nail matrix results of increase in both anteroposterior and lateral diameter of the nails.[1] Clubbed fingers have watch-glass nails with fingers looking like drumsticks. Historically, about 2,500 years ago Hippocrates is said to have first described clubbing in a patient with empyema. Clubbing is also called Hippocratic finger and is considered as one of the oldest clinical sign in medical practice.[2] Even though clubbed fingers are asymptomatic, clinical findings of clubbing is attributed to the presence of some chronic underlying diseases. Most often clubbing is thought to be associated with of chronic pulmonary diseases (mediastinal, neoplastic diseases etc.), disease of the cardiovascular system, endocrine disorders and some hepatobiliary gastrointestinal diseases etc., the exact pathogenesis of clubbing is not known; clinical relevance of clubbing still remains controversial.[3] Digital clubbing is primarily classified as primary (i.e., idiopathic, hereditary), or of secondary forms.

Clinically clubbing has been described as occurring in different grade/stages. Digital clubbing can present as bilaterally symmetrical or as unilateral involving a single digit. In the initial grade of clubbing, it is observed that there is a periungual erythema with softening of the nail bed, with a spongy sensation on palpation. With progression there is an increase beyond the normal 160° angle between the nail bed and the proximal nail fold. Eventually at the finger tip, the nail and periungual skin appear shiny with development of longitudinal ridge in the nail. As the grade advances the depth of the distal phalange increases with a possible hyper-extensibility of the distal interphalangeal joint. Clubbing generally develops over years but in certain conditions it may develop subacutely.[4] Anatomically, a simple physical examination with classic measurement of the Lovibond angle or the recent derived index of nail curvature, can be used to evaluate digital clubbing and monitor the dynamic process objectively.[5]

Digital clubbing is reported in approximately 80% of patients with lung cancer and other intrathoracic (pleural) tumours and mediastinal growth which contribute to 10% and 5% cases respectively.[6] Digital clubbing in lung cancer is one of the common paraneoplastic sign.[7,8] Most other reported cases have been with bone and soft tissues sarcomas, tumours of nasopharynx, and less commonly, tumours of uterus, cervix and renal cell carcinoma.[9–12]

Over years various hypotheses has been proposed in to explain the patho-physiology of digital clubbing, very little is known about this clinical entity. It

is hypothesized that in the pathogenesis of digital clubbing, local hypoxia, platelet activation, release of signal proteins like VEGF, and stimulation of angiogenesis and other escalated cellular activities are contributory to significantly higher plasma growth hormone levels serum transforming growth factor (TGF ß1), increased VEGF and platelet-derived growth factor, resulting in hypoxically regulated platelet aggregation in the digits.[13–17]

High-sensitivity C-reactive protein (hs-CRP) is one of the important cardiovascular event predictive inflammatory markers. Accumulating evidence suggests that inflammation is involved in the initiation and progression of cancer. There may be a link between inflammatory markers and cancer risk. High-sensitivity C-reactive protein, which is one of the most important systemic inflammatory markers, is produced mainly by hepatocytes in response to inflammatory stimuli.[18] Elevated hs-CRP levels have been documented in several conditions such as inflammatory disease, bacterial infection, fatal and non-fatal myocardial infarction, trauma, and surgery.[19] Elevated hs-CRP levels are also shown to be associated with increased risks of all-cause death.[20–23] Most studies on the influence of hs-CRP on cancer mortality have originated from western countries.[20–25]

The exact frequency of clubbing worldwide is not known. Even though clubbing is a commonly discussed and evaluated clinical sign, to date very limited information is available on the prevalence and its association with various types of cancers. Its clinical significance and impact on disease is not clearly understood. Association of clubbing in head and neck cancer has not been studied adequately.

Objectives of this study were to determine the relative frequency of digital clubbing in oral cancer and to evaluate the presence of inflammatory markers.

MATERIAL AND METHODS

The study was approved by Institute Ethics Committee (IEC). This was a case-control study. Cancer patients attending the Oncology Outpatient and their age matched control subjects, healthy relatives or attendants were included in the study. With informed consent the patients were grouped as Cases (patients with oral malignancy) and their normal healthy attendants/ relatives who were grouped as Controls. All subjects were evaluated clinically and a uniform protocol for clubbing evaluation was applied. Their habits, family history and any underlying coexisting disease were noted. The cancer patients underwent detailed primary disease and regional neck node evaluation, clinical and radiological evaluation with relevant blood tests and biopsy were undertaken. The patients were staged as per UICC TNM staging system. During clinical evaluation of the subjects specific evaluation of clubbing was performed. The protocol for grading clubbing was Grade I (G1): Softening of the nail bed (giving a spongy sensation on palpation), Grade II (G2): Obliteration of angle between nail and nail bed (increase in the normal 160 degree angle between the nail bed and the proximal nail fold), Grade III (G3): Parrot beak or drum stick appearance (swelling of the subcutaneous tissues over the base of nail causing overlying skin to become tense, shiny, increase in convexity), Grade IV (G4): Hypertrophic osteoarthropathy (painful swelling of wrist, elbow, knee, ankle with radiological evidence of subperiosteal new bone formation).

Blood samples (4 ml) were taken in plain tubes for analysis for hsCRP and was allowed to clot. The samples were then centrifuged and serum was separated using a micropipette and stored at -20 °C. hsCRP values were determined using Quantitative Immuno-turbidimetric method. The procedure was carried out at a wavelength of 540 ηm at a temperature of 37 °C with a cuvette length of 1 Cm on fresh serum samples. Absorbance A1 and A2 were taken at times 0 and 4 minutes and compared with the known calibrator values. For readings with absorbance >3.5, tests were conducted after diluting the samples by 1:2 or 1:5 with normal saline.

Statistical analysis was carried out using SAS 9.2, SPSS-15, Stata 10.1, MedCalc 9.0.1, Systat 12 and R Environment 2.11.1. For continuous variables Mean±SD (Range), and for categorical variables frequency and percentage were calculated. Student's *t*-test (two tailed, independent) was used on metric parameters, Chi-square/Fisher Exact test was used on categorical variables, and $p<0.05$ was taken as significant.

RESULTS

Over a period of 6 months, 72 subjects were recruited for the study, of which 36 were patients with proved malignancy (Cases) and 36 were normal healthy attendants (Controls) (Table-1). Male:Female ratio in Cases was 3:1 v/s 2.2:1 in Controls. Seventy-two percent of the patients were tobacco smokers compared to 27.8% in controls. Mean period of smoking in patients was 34 (20–50) years whereas normal healthy controls gave a history of smoking over 20.6 (20–40) years.

The frequency of primary and nodal stage of oral and oropharyngeal cancer was T2 8 (22%), T3 8 (22%), T4 20 (55.6%) with N0 7 (24%), N1 5 (17.2%), N2 14 (48%), N3 3 (10%). The clinical characteristics of cases and control are enumerated in Table-2.

In cancer patients clubbing was present in 26 (72.2%) compared to 8 (22.2%) in normal healthy Controls ($p<0.001$). Cancer patients with clubbing had 84.6% smokers among them compared to 70% of controls with clubbing (Table-3).

Table-1: Characteristics

Parameters	Cases (n=36)		Control (n=36)		*P*
	No	%	No	%	
Age group	59.33±10.05		59.06±9.69		p=0.905
40–50 yrs	6	16.7	4	11.1	
51–60 yrs	14	38.9	18	50	
61–70 yrs	12	33.3	9	25	
71–80 yrs	3	8.3	3	8.3	
81–90 yrs	1	2.8	2	5.6	
Male	27	75	25	69.4	p=0.599
Female	9	25	11	30.6	
Tobacco Smoking habit	26	72.2	10	27.8	p<0.001
Duration of Tobacco Smoking					
20–30 yrs	14	53.8	8	80	
31–40 yrs	5	19.2	2	20	
41–50 yrs	7	26.9	0	0	
Pan Chewing habit	15	41.7	5	13.9	
Duration of pan chewing habit					
10–20yrs	7	46.7	0	0	
20–40yrs	8	53.3	5	100	
Chewing tobacco & beetle nut	22	61.1	5	13.9	
Digital Clubbing	26	72.2	8	22.2	p<0.001
hsCRP	19.2			3.02	p<0.001

Table-2: Pattern of digital clubbing in study population

Digital Clubbing	Cases (Solid Tumour Oral & Oropharyngeal Cancer) n=36	Control (Healthy Subjects) n=36
Positive Clubbing	72.2% (26) (p<0.0001)	22.2% (8)
Clubbing Grade III-IV	9 (24%)	3 (8.3%)
Uni digital	1	
Grade I	6 (16.7%)	2 (5.6%)
Grade II	11 (30.5%)	3 (8.3%)
Grade III	9 (24.0%)	3 (8.3%)
Grade IV	0	0
Smokers with clubbing	84 %	40%

Table-3: Relationship between clubbing and smoking status in Cases

Clubbing	Smoking		Total (n=36)	*P*
	No (n=10)	Yes (n=26)		
Cases				
No	6 (60%)	4 (15.4%)	10 (27.7%)	<0.001
Yes	4 (40%)	22 (84.6%)	26 (72.2%)	
Control				
No	25 (96.2%)	3 (30%)	28 (77.8%)	<0.001
Yes	1 (3.8%)	7 (70%)	8 (22.2%)	
Total				
No	30 (83.3%)	6 (16.7%)	36 (50%)	<0.001
Yes	6 (16.7%)	30 (83.3%)	36 (50%)	

DISCUSSION

Though Hippocrates described this phenomenon of digital clubbing long ago and it is one of the commonest clinical sign to be elicited during routine clinical case history taking, the diagnosis, pathophysiology, and clinical relevance of clubbing still remains controversial.[3] Digital clubbing, can be an isolated clinical finding or may be found to coexist as part of the syndrome of hypertrophic osteoarthropathy (HOA-characterised by periostosis of long bones, joint pain, and clubbing)[4,5], it may be a primary clinical finding, also known as pachydermoperiostosis, or found to be an associated secondary feature to a variety of chronic disease processes.[6]

Inflammation has been linked with tumour development since 1863 with the discovery of leucocytes in neoplastic tissues. Rudolf Virchow described the role of inflammation in development of cancer. Since then, chronic inflammation has been considered as one of the risk factor for cancer. Patients with colon cancer have statistically significant higher serum CRP concentration. Anti-inflammatory drugs could lower colon cancer risk.[26–28]

Rice and Rowland in 1961 clinically described the ratio of the distal phalange to interphalangeal depth of more than 1:1 as a sign of digital clubbing. With the whole process taking years to develop, occasionally acute onset of digital clubbing has been observed.[3,29] Lovibond[30] described the sign Lovibond's angle. When the clinician viewed the finger from the lateral aspect, an angle of greater than 180 degrees made by the nail plate and its proximal nail fold can be used to differentiate true clubbing from other similar conditions, such as nail curving and paronychia. Leo Schamroth[31], an electro-cardiologist from Johannesburg, South Africa, described the sign that bears his name. He had experienced three episodes of infective endocarditis in 1975 and developed clubbing. His clinical findings were that the normal diamond-shaped window created by placing the dorsal surfaces of opposite terminal phalanges together was obliterated in clubbing.[32] The neoplastic causes of clubbing can vary from country to country. Data from North America shows 80% of acquired clubbing is associated with pulmonary disease.[33]

Various hypotheses have been proposed over years on Pathophysiology of Clubbing. Neurogenic, vagal stimulation causes vasodilatation, leading to clubbing. Clubbing is found to be associated and provoked by alterations in vascular dynamics in local arteriovenous anastamoses which allow blood to bypass capillaries to develop; these anastamoses are evolve into a neurohumoral end organs which allows the autonomic nervous system to regulate the digital microcirculation.[34]

In lung cancer many hypothesis have been postulated. Patients of bronchial carcinoma with clubbing had greater plasma growth hormone levels than patients with bronchial cancer without clubbing and control subjects without clubbing.[14] Dickinson and Martin[35] hypothesis has been the most promising, emerging evidence point at the physiology of platelet production, with megakaryocytes being found to normally fragment into platelets in the lungs. They

proposed that this processes disrupts the normal pulmonary circulation. Such situations are commonly observed in chronic lung inflammation, bronchial tumours, or intracardiac right-to-left shunts, wherein the disease process would allow the whole megakaryocytes to enter the systemic circulation and by virtue of their large size, cause them to get impacted in the fingertip circulation. Megakaryocytes and megakaryocyte fragments are activated to release platelet-derived growth factor (PDGF) locally in the finger tip. PDGF promotes growth, vascular permeability, and monocyte and neutrophil chemotaxis, and leading to an increased number of vascular smooth muscle cells and fibroblasts, all of which are seen in the pathology of clubbing. Dickinson and Martin[35] have pointed out that inflammatory bowel disease is often associated with a thrombocythemia and liver disease can be accompanied by pulmonary arteriovenous malformations. The megakaryocyte/platelet theory in the pathogenesis of clubbing has been evaluated and supported by several subsequent studies. Another platelet-derived, growth-promoting cytokine, vascular endothelial growth factor, is found to be elevated in the serum of patients with lung cancer, which is likely to contribute to the vascular hyperplasia seen in clubbing pathology.[36]

Pokley MI *et al* in 1991 have demonstrated that oestrogen synthesis was increased in cancer of oesophagus.[37] Digital clubbing is said to be the result of hypertrophy of connective tissues and increased vascularity of the distal phalanges. Recent data suggests that development of clubbing is due to the presence of a bioactive substance in the systemic circulation, which is either overproduced or poorly eliminated by the affected organ.[38]

Erlinger *et al* reported that plasma CRP concentrations was found to be higher in colorectal cancer patients compared to control subjects.[39] Otake *et al*[40] indicated that the multivariate-adjusted odds ratios of large adenomas for the lowest to highest categories of CRP were 1.00, 1.81, 1.61, and 2.21 respectively. McSorley *et al*[41] demonstrated increasing risk with increasing concentration of CRP.

CONCLUSIONS

Digital clubbing is one of the commonly evaluated clinical sign. Its strong association with chronic disease like cancer and its implications is still a clinical enigma. A significant association of clubbing and tobacco smoking was observed in head and neck cancer patients.

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