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RESEARCH ARTICLE

HISTOPATHOLOGICAL EVALUATION OF CHRONIC NON HEALING ULCERS OF SKIN IN PATIENTS REFERRED TO TERTIARY CARE HOSPITAL IN KASHMIR.

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Keywords:-

Non-healing ulcer, malignant, benign, squamous cell carcinoma, neuropathic diabetic ulcer, tuberculosis.

Abstract

Background: Skin is the single largest organ of the body that protects against mechanical trauma, radiation and infection. Because of its complexity a wide range of diseases can develop from the skin ranging from infectious diseases to malignancy, some of which may present as non-healing ulcers. Non healing ulcers are an important cause of morbidity in developing countries. Study of non-healing skin ulcers is challenging and at times even frustrating than any other skin lesions. This study was taken keeping in view the present scenario were patient with non-healing ulcers go unnoticed for a long time without biopsy resulting in uncertainty of developing malignancy which can otherwise be identified at a very early stage by early histopathological examination.

Aim: Aim of this study was to study the histopathological outcome of non-healing ulcers in this geographical area where much is not known about the etiology of non-healing ulcers.

Methodology: This study was hospital based two years prospective study extending from January 2016 to December 2017 conducted in Department of Pathology, Government Medical College Srinagar. During this period patients referred from peripheral hospitals with ulcers that had not healed for 4 weeks or more after conventional therapies were included in this study. The detailed history and clinical examination findings were retrieved from the case files. Biopsies received were processed as per the standard protocol and slides were examined by the senior pathologist in the Department of Pathology, Government Medical College Srinagar.

Results: During the two years period department received biopsies from 282 patients with non-healing ulcers. Out of 282 patients 180 were males and 102 were females with a M:F ratio of 1.76:1. Out of the 282 cases 100 (35.46%) were diagnosed as malignant ulcers and 182(64.54%) were diagnosed as benign ulcers (Table 1). Out of the 282 cases, 70 cases (24.82%) were found to be neuropathic diabetic ulcers, 52 (18.43%) were diagnosed as tubercular ulcers, 44 (15.60%) as infectious, 4 (1.42%) as leprosy, 4 (1.42%) cases were due to parasitic infection (cutaneous leishmaniasis) and 8 cases (2.83%) as others. Benign ulcers were found to be fairly common below 50 years

of age. Lupus Vulgaris was found to be the commonest form among the tubercular ulcers constituting 75% of the tubercular ulcers followed by Scrofuloderma accounting for 25% of the cases. Among malignant cases, that Squamous cell carcinoma is the most common variety of malignancy encountered in an ulcer accounting for 82% of cases followed by Basal cell carcinoma 14% and malignant melanoma 4%.

Conclusion: Non-healing ulcers can be encountered at any age and etiology may vary from one geographical region to other and may also be different in different racial groups. Thus beside a good clinical diagnosis, early biopsy to rule out malignancy and identify the etiology is mandatory for a better outcome and minimize the morbidity and mortality among patients with non-healing ulcers.

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Introduction:-

Skin is the single largest organ of the body that protects against mechanical trauma, radiation and infection. Because of its complexity a wide range of diseases can develop from the skin ranging from infectious diseases to malignancy, some of which may present as non-healing ulcers¹.

General surgical referral guidelines defines any non-healing ulcer as that which has been present for 3-4 weeks duration and has not responded to conventional therapies¹. Sometimes a need of surgical intervention is forced upon. Although histopathology remains the gold standard for most dermatologic diagnoses, it must be recognized that not all lesions are amenable to definitive "specific" histologic diagnosis².

Chronic wounds are characterized clinically as wounds that have failed to proceed through a biologically predictable and timely healing process and either are unresponsive to initial therapy or persist following appropriate wound care²⁻³. They are often identified by the presence of a raised, hyperproliferative, yet nonadvancing wound margin^{2,3}. Understanding the pathological alterations of wound tissue that are refractory to standard wound therapy is essential for effective wound management and healing. The presence of a chronic wound can result in significant morbidity or mortality.

Chronic cutaneous ulcers are common in the developing countries like India, especially in rural areas with poor living conditions. These ulcers often result from trauma, vascular insufficiency, neuropathy, leprosy, diabetes, malignancy or hemoglobinopathies¹. If poorly managed these lesions may undergo malignant transformation⁴⁻⁶.

Thus, the study of non-healing skin ulcers is challenging and at times even frustrating than any other skin lesions. This study was taken keeping in view the present scenario where patient with non-healing ulcers go unnoticed for a long time without biopsy resulting in uncertainty of developing malignancy which can be identified at a very early stage by early histopathological examination.

Material And Methods:-

This study was hospital based two years prospective study extending from January 2016 to December 2017 conducted in Department of Pathology, Government Medical College Srinagar. During this period patients referred from peripheral hospitals with ulcers that had not healed for 4 weeks or more after conventional therapies were included in this study. The detailed history and clinical examination findings were retrieved from the case files. Biopsies received were processed as per the standard protocol and slides were examined by the senior pathologist in the department.

Results:-

During the two years period department received biopsies from 282 patients with non-healing ulcers. Out of 282 patients 180 were males and 102 were females with a M:F ratio of 1.76:1. Out of the 282 cases 100 (35.46%) were diagnosed as malignant ulcers and 182 (64.53%) were diagnosed as benign ulcers (Table 1).

Table 1:- Etiological types of Non-healing ulcers.

Etiological type	Number of patients	Percentage
Malignant ulcers	100	35.46%
Neuropathic diabetic ulcers	70	24.82%
Tubercular ulcers	52	18.44%
Infectious ulcers	44	15.60%
Leprosy	4	1.42%
Cutaneous leishmaniasis	4	1.42%
Others	8	2.84%
Total	282	100%

Out of the 282 cases, 70 cases (24.82%) were found to be neuropathic diabetic ulcers, 52 (18.43%) were diagnosed as tubercular ulcers, 44 (15.60%) as infectious, 4 (1.42%) as leprosy, 4 (1.42%) cases were due to parasitic infection (cutaneous leishmaniasis) and 8 cases (2.83%) as others. Benign ulcers were found to be fairly common below 50 years of age. Lupus Vulgaris was found to be the commonest form among the tubercular ulcers constituting 75% of the tubercular ulcers followed by Scrofuloderma accounting for 25% of the cases. Among malignant cases, that Squamous cell carcinoma is the most common variety of malignancy encountered in non-healing ulcer accounting for 82% of cases followed by Basal cell carcinoma 14% and malignant melanoma 4%.

Swabs from wound of 44 patients diagnosed as infectious ulcers were sent for culture and sensitivity tests, Staphylococcus was found to be the most common pathogen accounting for 50% of the bacteriological isolates. This was followed by klebsiella (16.67%), Proteus (16.67%) and Pseudomonas and Streptococcus was seen in 8.33% each. The group of "other ulcers" consist of venous ulcers which were diagnosed clinically and radiologically but no histopathological evidence could be found, ulcers due to foreign body granuloma histopathologically and ulcers for which no etiology could be identified histologically. Hence these ulcers could not be typified in definite etiological classes and were grouped together as others.

Discussion:-

Non healing ulcers are an important cause of morbidity in developing countries^{7,8}. This may be explained by the poor socioeconomic conditions, poor health services in remote areas and lack of public awareness. In contrast with the developed countries, little is known about the prevalence and etiology of non-healing ulcers in these areas. One study from Nigeria reported that the most common etiologic factors were trauma, diabetes mellitus and sickle cell disease⁹ Depending on the region, infectious causes such as cutaneous Leishmaniasis or Buruli ulcer may be encountered^{10,11}.

In contrast venous ulcers are most common cause of ulcers in developed countries but are reported to be uncommon in tropical countries¹², Zeegelar et al¹³ also reported that venous ulcers and diabetic ulcers are common in developed countries. In his study we found that the most common cause of non- healing ulcers in this region are malignant ulcers found in 100 patients (35.46%) followed by neuropathic diabetic ulcers 70 patients (24.82%), Tuberculosis in 52 patients (18.43%), Infectious causes were found in 44 patients (15.60%), Leprosy in 4 patients (1.42%), Cutaneous Leishmaniasis in 4 patients (1.42%) and other causes in 8 patients (2.84%). Results of our study were different from western studies where venous ulcers were found as most common cause by Mekkes et al¹⁴. Zeeglar et al¹³ in his study found infectious causes followed by malignancy as the most common cause of non-healing ulcers. Results of our study were similar to studies from India by Sarkar PK¹² and Saraf SK³². The differences from western studies may be due to different geographical location, tropical climate, poor health services, different racial group and illiteracy, ignorance.

In the present study, malignant ulcers were found to be the most common cause of non-healing ulcers of skin accounting for 35.46%. Of these squamous cell carcinoma is the most common 82% cases followed by Basal cell carcinoma (14%) and Malignant melanomas (4%). This finding is in concordance with that reported by Yakubu et al¹⁵. No venous or arterial ulcers were found histologically. However, two cases of venous ulcers were found which were diagnosed clinically and radiologically but no specific histologic features were identified to typify them, hence these were grouped under "other ulcers". Among the malignant ulcers Squamous cell carcinoma is the most common. Patients with non-healing ulcers for more than two years usually had malignant ulcers. Similar conclusions were drawn by Singh et al¹⁶, Talvalkar et al¹⁷, Schreiber et al¹⁸ and Adinarayan M et al¹⁹. In the present study 11

patients presented with Marjolin's ulcer, and were confirmed histopathologically as Squamous cell carcinoma. This is in concordance with the conclusion drawn by Morra and colleagues²⁰ and Jellouli & colleagues²¹.

It was observed that common age group for malignant ulcer was 60-70 years followed by 50-60 years with a male preponderance. Similar conclusions were drawn by Singh et al¹⁶. Also malignancy below the age of 40 years was rare, only 4 cases were detected. This matches with that reported by Singh et al¹⁶ who found 4 cases below the age of 30 years.

We observed neuropathic diabetic ulcers as the second common cause for non-healing ulcers, accounting for 24.82% of the non-healing ulcers. This is in accordance with studies by Neil et al³³ who found that approximately 20% of all non-healing ulcer related admissions in UK were due to diabetic foot ulcer disease. Alex and colleagues also reported an incidence rate that ranged from 8%-17%. The above studies are in contrast to the figures reported by Ch. Manes et al³⁴ and Nyamu et al³⁵ being 4.75% and 4.6% respectively.

The present study also observed two age peaks in presentation of the patients with non-healing ulcers due to diabetes. The first peak is in the 6th decade accounting for 38.5% of the patients and the 2nd peak is in the 5th decade accounting for 30.8% of the patients. The studies by Bansal et al³⁶ and Neil et al³³ reported similar age incidences. Diabetic ulcers were relatively common in males accounting for 61.5% and less common in females accounting for 38.5%. This is similar to Gaur et al³⁷ who reported a male to female ratio of 1.2:1. However Ch. Manes et al³⁴ did not establish different rates between male and female population.

This was followed by tubercular ulcers 18.44%. Although this is in contrast to the conclusion drawn by M. Naveduz Zafar et al²², Binod Kumar Thakur and colleagues²³ and Padmavathy and colleagues²⁴ who reported incidence of cutaneous Tuberculosis of 3.62%, 0.25% and 1.6% of all skin biopsies respectively but in their studies they have taken all skin biopsies and in the present study we have included cases which have presented with non-healing ulcers only.

In the recent years, with the emergence of anti-Tubercular drug resistant strains and AIDS epidemic, there is a worldwide rise in the incidence of Tuberculosis. More so in the poverty struck areas of the world due to poor nutrition, poverty, non-availability of diagnostic aids and treatment, over-crowding, ignorance about the disease, rise in immunosuppressive therapy, decline in Tuberculosis control efforts and emergence of resistant strains of Mycobacterium tuberculosis have amplified the situation^{25,26}.

Among the Tubercular ulcers most patients presented at the 2nd & 3rd decades which was in accordance with Binod Kumar Thakur and his colleagues²³. Padmavathy and colleagues also reported a similar observation²⁴. Lupus Vulgaris was found to be the most common form followed by Scrofuloderma. Similar to this study, M. Naved uz Zafar et al²² also reported Lupus Vulgaris as the most common form. Similar results were seen by Satyanarayan²², Singh et al²⁸ and Kumar et al²⁹ our study we could demonstrate Acid Fast Bacilli (AFB) in 19% of patients by Ziehl Neelsen staining (ZN stain) method in pathological sections, this is similar to studies by M. Naveduz Zafar et al²² who found AFB in 18.42% cases and Ranjan Agarwal et al³¹ who found AFB in 17.19% cases but is not in accordance with the results of Mahaisavariya et al³⁰ who found AFB in 30.77% cases.

In the present study non-healing ulcers due to infectious etiology accounts for 15.60%. Bacteria are the main cause among the infectious ulcers in our setting; culture and sensitivity were performed Staphylococcus being found as the most common causative agent accounting for 50% of the infectious causes followed by Klebsiella 16.67%, Proteus accounting for 16.67%, Pseudomonas and Streptococcus accounting for 8.33% each. These results are in accordance with the results reported by J. E. Zeegalaar et al³⁸.

In similar studies by Tan et al³⁹, Erikson et al⁴⁰ and Giacometti et al⁴¹ reported Staphylococcus as the most common organism.

However other studies by Gaur et al³⁷ reported Enterococcus as the most common organism and the study by Bansal et al³⁶ reported pseudomonas as the most common organism.

The reason for such discrepancy could not be assessed but may be due to the environmental factors and the intrinsic properties of the microorganism themselves as reported by Diana et al⁴² and Mrek et al⁴³.

Summary and Conclusion:-

The most common cause of non-healing ulcers in this geographical area was found to be malignancy (35.46%). The other causes identified were Neuropathic Diabetic ulcers (24.82%), Tubercular ulcers (18.44%), and Infectious Ulcers (15.60%), Leprosy (1.42%), Cutaneous Leishmaniasis (1.42%) and other ulcers (2.84%). Among the malignant ulcers, Squamous cell carcinoma is the most common form (82%); followed by Basal cell carcinoma (14%) and Malignant Melanoma (4%). Lupus vulgaris was found to be the most common form (75%) followed by Scrofuloderma (25%) among tubercular ulcers. Diabetic ulcers were found to be more common in the age group of 50-60 years. Males are commonly affected. Staphylococcus was the most common organism isolated (50%) followed by Klebsiella (16.67%), Proteus (16.67%), Pseudomonas (8.33%) and Streptococcus (8.33%).

Thus it can be concluded from the study that non-healing of ulcers can be encountered at any age and etiology may vary from patient to patient, one geographical region to other and may also be different in different racial groups. Thus beside a good clinical diagnosis, early biopsy to rule out malignancy and identify the etiology is mandatory for a better outcome and minimize the morbidity and mortality among patients with non-healing ulcers.

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