Clinical profile of cutaneous manifestations with and without hematologic disease: A comparative study

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ABSTRACT

Aim: The aim was to study the clinical profile of cutaneous manifestations of hematologic disorders and to compare it with that of non-hematologic disorders. **Materials and Methods:** Cutaneous manifestations of hematologic diseases fall in seven well-defined categories. A total of 153 outpatients with skin manifestations fitting in these categories were enrolled in a comparative study of 1-year duration. Clinical profile of these cutaneous manifestations was studied and any underlying hematologic disorder was ruled out with the help of a hematologist. Difference in the clinical profile of cutaneous manifestations with and without hematologic diseases was studied. **Result:** Of the 26,174 outpatients during the study period, 153 had cutaneous manifestations fitting in the categories of hematologic disorders. Of these 153 patients, 33 had hematologic disease as the cause of their cutaneous manifestation (21.57%), whereas 78.42% had no hematologic disorder. Disorders of hemostasis formed the largest group (36%) followed by cutaneous deposits/infiltrations (15%), vesiculobullous disorders (6%), and cutaneous vasculitis (9%) were least commonly associated with hematologic disorders. **Conclusion:** Hematologic diseases are associated with complex array of cutaneous manifestations. The incidence of hematologic disease–associated cutaneous manifestations was 0.13%. Findings of this study will help dermatologists and physicians with the early recognition of cutaneous signs of hematologic disorders.

Key words: Cutaneous, hematologic, purpura

INTRODUCTION

Hematology includes study of blood and blood-forming tissues. Given the large number and variety of hematologic disorders, it is not surprising that mucocutaneous manifestations of hematologic disorders are not uncommon.[1] Not all the patients with hematologic disorders present with hematologic problems, but many of them can have dermatologic manifestations. Cutaneous signs aid in the early diagnosis and treatment of hematologic disorders, hence necessitating a study of such correlation. Hematologic disorders not only cause recurrent skin lesions but also form a major group of recalcitrant skin lesions. Although individual case reports are available in the published literature, comparative study of cutaneous manifestations of hematologic disorders has not been reported to the best of our knowledge. Our study was aimed to determine the incidence of cutaneous alterations in patients with hematologic disorders and to study their profile.

MATERIALS AND METHODS

The study was carried out at the Dermatology department of a tertiary referral centre over one year. All patients attending the Outpatient Department (OPD) (irrespective of age, gender, etc.) were screened and only those satisfying the inclusion and exclusion criteria were enrolled in the study.

As described by Piette *et al.*, skin manifestations with hematologic associations fall in the following categories[1]: (i) purpura, (ii) recurrent cutaneous infections (more than four episodes of cutaneous infections in 1 year), (iii) neutrophilic cutaneous reactions, (iv) vesiculobullous diseases, (v) skin cancers, (vi) vasculitis, (vii) ulcerations (excluding genital ulcers due to sexually transmitted infections and oral ulcers alone), and (viii) cutaneous deposits/infiltrations. Patients with these manifestations formed an inclusion group. Patients of leukocytoclastic vasculitis were included under vasculitis group

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and not as neutrophilic cutaneous reactions. The study included only those patients seeking dermatologist's consultation on an outpatient basis. Diagnosed cases of hematologic diseases with skin manifestations, referred to dermatology OPD by hematologists, were also included. However, skin manifestations related to the treatment of hematologic disorders and those outside the above-mentioned categories were excluded.

Complete clinical examination and relevant investigations were done to prove or rule out hematologic association of a given cutaneous manifestation. The profile of cutaneous manifestations associated with hematologic disease was compared with those without hematologic disease. These patients attended the skin department during the same period of time. As the prevalence of cutaneous manifestations not associated with hematologic diseases is more, obtaining age and gender-matched controls for the purpose of comparison was not possible in this cross-sectional study.

Permission to conduct the study was obtained from the institutional ethics committee. Statistical analysis was done using Chi-square test or Fisher's exact test and two-tailed test. $P < 0.05$ was considered to be statistically significant.

RESULTS

Of the 26,174 patients who attended Dermatology OPD during the study period, 153 had cutaneous manifestations conforming to the categories as described by Piette *et al*. for hematologic disease. Of these, 33 had associated hematologic disease with an overall OPD incidence of 0.13%. Table 1 summarizes the distribution and demographic data of patients with cutaneous manifestations in both the groups.

Of the 33 patients with hamatologic disease, thrombocytopenic purpura (50%) was the most common bleeding disorder followed by disorders of coagulation (33.33%). Petechiae were the most common skin manifestation (58.3%) followed by noninflammatory retiform purpura (33.3%) [Figure 1] and hematoma (16.6%). The average platelet count in patients with petechiae was 48,000/mm^3 (range, 40,000-74,000/mm^3). In the nonhematologic group, 17 patients had pigmentary purpuric dermatoses (PPD), four had corticosteroid-induced purpura, and two patients had senile purpura.

Hematologic disorders associated with recurrent cutaneous infections were uncommon diseases like hyperimmunoglobulin E (hyper-IgE) syndrome, acute lymphocytic leukemia, hemosiderosis-associated scurvy, and factor XIII deficiency. In the nonhematologic group, 43% (6/14) patients had recurrent infections due to diabetes mellitus, whereas 29% (4/14) were attributed to human immunodeficiency virus infection. Bacterial infections of the skin predominated in both the groups (75% and 90%) in which *Staphylococcus aureus* was the most commonly isolated organism. Most common presentation of neutrophilic dermatoses in our study was plaques and nodules in both the groups (hematologic 100% vs. nonhematologic 66%).

In vesiculobullous disorders, we noted two cases of paraneoplastic pemphigus (PNP), both secondary to Castleman's disease [Figure 2]. Both cases of PNP were confirmed on the basis of the type of cutaneous presentation, histopathology, and indirect immunofluorescence. The site of Castleman's disease was identified as suprarenal adrenal glands by computed tomography scan of the abdomen. Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) contributed to 65% and 35% of the total skin cancers, respectively. Head, neck, and face (88.8%) was the most common site of BCC, whereas SCC was most commonly found over extremities and genitals. None of the patients of skin cancers had associated hematologic malignancies, such as Hodgkin's lymphoma. In cutaneous vasculitis group, the classical triad of Henoch–Schönlein purpura was noted in 20% of the cases. Clinical and laboratory findings are stated in table 2. In the hematologic group, five patients had cutaneous deposits/

Figure 1: Geographic area of cutaneous infarction in purpura fulminans

Figure 2: Oral hemorrhagic crusting in paraneoplastic pemphigus

Table 1: Distribution of the patients in all categories of hematologic diseases

Cutaneous manifestations of hematologic disease	With hematologic disorder	Without hematologic disorder	P value, OR, and CI
Purpura (*n*=35)	12	23	*P*=0.03, OR 2.41, CI 0.96–6.00
Mean age (in years) ±SD	20.2±4.12	36±5.34	
Average duration of illness	18.9 days	2 years	
Gender	M-6, F-6	M-12, F-13	
Recurrent cutaneous infections (*n*=18)	4	14	*P*>0.05
Mean age (in years) ±SD	13.7	44.6	
Average duration of illness	13 months	1.6 months	
Gender	M-1, F-3	M-10, F-4	
Neutrophilic cutaneous reactions (*n*=8)	2	6	*P*=0.05
Mean age (in years) ±SD	55	38.3	
Average duration of illness	0.5 months	30.6 months	
Gender	M-2, F-0	M-2, F-4	
Vesiculobullous disorders (*n*=23)	2	21	*P*=0.05
Mean age (in years) ±SD	20.5	46.9	
Average duration of illness	13 months	5.3 months	
Gender	M-1, F-1	M-7, F-14	
Skin cancers (*n*=14)	0	14	*P*=0.02 (Fisher's exact test)
Mean age (in years) ±SD	-	54.5	
Average duration of illness	-	2.5 years	
Gender	-	M-8, F-6	
Vasculitis (*n*=20)	3	17	*P*>0.05
Mean age (in years) ±SD	43.3	27.4	
Average duration of illness	4 years	13.4 days	
Gender	M-1, F-2	M-8, F-7	
Ulcerations (*n*=28)	5	23	*P*>0.05
Mean age (in years) ±SD	39.4	48.4	
Average duration of illness	5 months	24.4 months	
Gender	M-0, F-5	M-14, F-9	
Cutaneous deposits/ infiltrations (*n*=19)	5	2	*P*=0.001, OR 10.54, CI 1.68–83.33
Mean age (in years) ±SD	34	2	
Average duration of illness	4 months	2 months	
Gender	M-3, F-2	M-1, F-1	
Total (n=165)	33	120	

OR: Odds ratio, CI: Confidence interval, SD: Standard error

infiltrations in the form of cutaneous mastocytosis (two cases), leukemia/lymphoma cutis (two cases), and a rare case of myeloma-associated primary systemic amyloidosis [Figure 3]. In the nonhematologic group, two patients had cutaneous metastasis secondary to adenocarcinoma of the lung and adenocarcinoma of the breast.

DISCUSSION

In this study, except for the purpura group, hematologic disorders were found to be insignificantly associated with cutaneous manifestations in patients attending dermatology out-patient department (OPD).

Disorders of hemostasis formed the largest group of hematologic disorder with dermatologic manifestations. This was evident because disorders of hemostasis manifest directly into the skin either as bleeding or thrombosis of dermal vasculature. It was found most commonly in the age group of 0-10 years (50%). This was due to high incidence of hereditary disorders of platelets, disorders of coagulation, and postinfectious purpura fulminans in children that contributed to 33% of cases in this study. The

morphologic expression of disorders of hemostasis correlated well with the nature of underlying disease. Average platelet count in thrombocytopenic purpura was found to be 48,000/mm^3. This correlates well with the fact that spontaneous hemorrhages in the skin in the form of petechiae occur when the functional platelet count is in the range of 10,000-50,000/mm^3[2]. None of

Table 2: Clinical and laboratory profile of patients with leukocytoclastic vasculitis

Clinical characteristics	With hematologic diseases (*n*=3) (%)	Without hematologic diseases (*n*=17) (%)
Pruritus as presenting symptom	0 (0)	6 (35)
Pain as presenting symptom	0 (0)	6 (35)
Asymptomatic	3 (100)	5 (30)
Fever	0 (0)	6 (35)
Hematuria/melena	0 (0)	3 (18)
Abdominal pain	0 (0)	7 (41)
Palpable purpura	2 (67)	17 (100)
Ankle edema	1 (33)	6 (35)
Distribution on lower extremities alone	0 (0)	9 (53)
Distribution on both upper and lower extremities	3 (100)	6 (35)
Partial response to treatment	2 (66.6)	2 (12)
Raised serum IgA levels (>450 mg%)	2 (67)	6 (35)
Urine albumin+	1 (33)	8 (47)
24 h urine protein>0.5 g/day	1 (33)	4 (24)
Low C3/C4	1 (33)	0 (0)
Cryoglobulins+	1 (33)	0 (0)
Urine RBCs+	0 (0)	3 (18)

IgA: Immunoglobulin A, RBCs: Red blood cells

Figure 3: Waxy smooth papules of myeloma-associated primary systemic amyloidosus

the patients of thrombocytopenic purpura in our study developed severe complications, such as subarachnoid hemorrhage, intracerebral or gastrointestinal bleeding, which usually occur when functional platelet count falls below 10,000/mm^3. Our findings cannot be compared with previous studies as no such study has been reported in the published literature. This study underscores the fact that the skin features serve as an early marker of disorders of hemostasis. Similarly, morphology of cutaneous purpura can help in arriving at a definite diagnosis.

Prevalence of recurrent cutaneous infections (RCI) due to hematologic disorders was lower as compared with those without hematologic disorders. The average age at the time of presentation was 13.7 years in hematologic group, whereas 44.6 years in the non-hematologic group, implying that recurrent cutaneous infections due to hematologic disorders occur at a younger age than those without hematologic disorders. Common hematologic causes of RCI include qualitative and quantitative disorders of neutrophils. Causes of neutropenia (counts <500 cells/μL) include congenital and cyclic neutropenia, leukemia, lymphoma, marrow toxicity, marrow failure, infiltration, and immune and autoimmune neutropenia. Functional leukocyte defects responsible for RCI are Chediak–Higashi syndrome, Griscelli syndrome, chronic granulomatous disorders of childhood, myeloperoxidase deficiency, C3 deficiency, hyper-IgE syndrome, Wiskott–Aldrich syndrome, and Leiner's disease. Many of these disorders are associated with specific skin manifestations in addition to RCI.

The most common presentation of neutrophilic dermatoses in our study was plaques and nodules in both the groups (hematologic 100% vs. nonhematologic 66%). In hematologic diseases, two cases of Sweet's syndrome were noted, one of which was associated with chronic myeloid leukemia [Figure 4] (although Sweet's syndrome is most commonly described with acute myelogenous leukemia) and the other with carcinoid tumor (an association not reported in the literature). Classically described features of malignancy-associated Sweet's syndrome such as ulcerations and vesiculations in the plaques, oral ulcers, and recurrent disease were not seen in our patients.

In vesiculobullous disorders, both the cases of paraneoplastic pemphigus were associated to the Castleman's disease, the association that is well reported in the literature. Recalcitrant oral erosions, lip crusting, polymorphic skin lesions, and paronychia in both the cases were characteristic findings, similar to that reported by Anhalt *et al.*[3] Both cases of paraneoplastic pemphigus were below 25 years of age, whereas most of the previously reported cases of paraneoplastic pemphigus associated with Castleman's tumor by Fried *et al.*,[4] Rybojad *et al.*,[5] and Su *et al.*[6] showed that the disease commonly develops between the 5th and the 8th decade. The average duration of the illness at the time of presentation was 5.3 months in the control group as compared with 13 months in the study group.

Figure 4: Multiple erythematous and edematous plaques of chronic myeloid leukemia -associated Sweet's syndrome

In skin cancers group, none of the patients had associated hematologic malignancies such as Hodgkin's or non-Hodgkin's lymphoma, although the association has been mentioned in the literature. Expectedly in the control group, skin cancers were more common in old-aged individuals. Although cases of BCC following radiotherapy for Hodgkin's disease[7] and mycoses fungoides in association with B-cell malignancies[8] are reported, there is no reported association of BCC or SCC with lymphoproliferative malignancies. Our study confirms the similar weak association of BCC and SCC with lymphoproliferative malignancies.

In vasculitis group, cause could not be ascertained in the majority (50%) of the cases of leukocytoclastic vasculitis (LCV). Patient with cryoglobulinemia-associated LCV had transient palpable purpura over upper extremities and trunk. Both patients of benign hypergammaglobulinemic purpura (HGP) of Waldenstrom showed benign IgG monoclonal gammopathy as evidenced by serum electrophoresis. One of the patients of HGP showed positive Ro/SSA antibodies, positive rheumatoid factor, and positive Schirmer test indicative of Sjogren's syndrome (secondary HGP). Study of nine patients of HGP by Miyagawa et al.[9] found antibodies to

Ro/SSA in 7 patients (78%), whereas in another study of 18 patients by Invernizzi et al.[10] antibodies to Ro/SSA were found in all patients (100%). Serum IgG was elevated in both patients (100%), which correlated with similar observations made by Miyagawa et al. in a study of nine patients (100%) of HGP. Although the other patient did not have associated disease, studies by Kyle et al.[11] and Zaharia et al.[12] emphasize that associated diseases can develop 10 or more years after the onset of HGP and cannot ever be completely excluded. Sanchez-Guerrero et al.[13] reported 5% incidence of LCV associated with malignancies in a study of 11 cases, whereas we did not observe malignancy-associated LCV. The highest incidence of LCV in children (47%) in the control group (age group, 10–20 years) could be because of the increased occurrence of streptococcal throat infections in children. The elevation of serum immunoglobulin A levels in 35% patients of LCV, not associated with hematologic disorders is in contrast with that reported in an Indian study by Mittal et al.[14] in which the serum immunoglobulin levels were estimated in 30 cases of cutaneous vasculitis and elevated levels of immunoglobulins in 19 cases (63.3%), low levels in four cases (13.3%), and normal levels in seven (23.3%) were observed. Recurrence rate was 66.6% in the study group as against 14.2% in the control group, indicating poor prognosis of LCV in cases associated with hematologic disorders.

Hematologic causes of skin ulcerations include red blood cell disorders (sickle cell anemia, thalassemia, hereditary spherocytosis, paroxysmal nocturnal hemoglobinemia), polycythemia vera, essential thrombocythemia, cryoglobulinemia, leukemia, lymphoma, some histiocytoses, antiphospholipid antibody syndrome, heparin necrosis, protein C deficiency, hyper-IgE syndrome, neutropenia, reactive hemophagocytic syndrome, neutrophilic dermatoses, Kaposi's sarcoma, and lymphomatoid papulosis.[1] In our study, hematologic diseases such as purpura fulminans, antiphospholipid antibody syndrome, xanthoma disseminatum, and beta-thalassemia presented with ulcerations. Vasculitic ulcers formed the largest control group (30%) and the female preponderance (63%) was noticeable in the control group. Other causes of ulcerations in the control group were attributed to Hansen's disease (22%), malignant ulcers (18%), venous ulcers (17%), and tuberculous ulcers (13%). Ulcers due to hematologic disorders presented at an early age.

In summary, the results of this comparative study present useful and interesting data on the incidence and spectrum of cutaneous manifestations of hematologic disorders as observed in patients attending the Dermatology OPD. Hematologic disorders were responsible for a minority of cutaneous manifestations. However, these data should eventually be helpful to make dermatologists and physicians aware of cutaneous signs of hematologic diseases for early diagnosis, treatment, and timely referral to relieve suffering and decrease

morbidity and mortality. More controlled studies of larger sample size are needed to validate the findings observed in our study.

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