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Periungual Desquamation in Patients with Kawasaki Disease

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Keywords

periungual desquamation; Kawasaki disease; coronary artery aneurysm

Introduction

In the original report of 50 Japanese patients, Dr. Kawasaki noted periungual desquamation of the fingers and toes in all but one of his patients in the second week after onset of fever(1,2). This often dramatic, full-thickness epidermal peel has become a hallmark of KD and often prompts health care providers to consider the diagnosis of missed KD in a child with an antecedent febrile illness, despite the fact that the sensitivity and specificity of this clinical sign are unknown. Because the desquamation is usually first noted after the patient has been discharged from the hospital, clinical series in which different physicians see the patient in the outpatient setting may not yield reliable estimates of the frequency of this physical finding. We took advantage of a patient series in which a single pediatrician evaluated all KD patients in a 5-year period in both the in-patient and outpatient setting.

Methods

We performed a retrospective review of all patients diagnosed with KD between 2003 and 2007 who were treated on or before the 10th day after fever onset (Illness Day 10) at Rady Children's Hospital San Diego. To meet the enrollment criteria, subjects must have been febrile for at least 3 days but not more than 10 days and must have met 4 of the 5 standard clinical criteria for KD or met 3 of 5 criteria with at least one dilated coronary artery (internal diameter ≥2.5 standard deviations from the mean normalized for body surface area (Z score)) as determined by echocardiography(3,4). Aneurysms were defined as a focal region of the coronary artery 1.5 times the diameter of the adjacent segment. All patients were examined in the hospital and in the KD clinic by a single pediatrician (JCB). Every patient had at least one follow-up visit between 2 and 4 weeks after hospital discharge. In the outpatient clinic, parents were interviewed regarding periungual desquamation of the fingers and toes. Examination of the digits was performed with a lighted magnifying glass to detect desquamation, the presence or absence of which was described in the dictated clinic notes. Demographic and laboratory data were obtained prospectively for every patient and entered into an electronic database and downloaded as an Excel file for analysis. Patients were divided into two groups based on presence or absence of desquamation. Clinical findings, laboratory results, response to IVIG, and coronary artery outcome were compared between the two groups using Wilcoxon Rank-

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Sum test for continuous variables, and Chi-Square or Fisher's Exact test for comparison of proportions for categorical variables. Tests were two-sided with a significance level of $p < 0.05$. Multivariate logistic regression assessed the independent contribution of variables identified in the univariate analysis to differences between the groups. All statistical analyses were performed with NCSS/PASS software (Number Cruncher Statistical Systems. Kaysville, Utah. WWW.NCSS.COM).

Results

A total of 243 patients during the 5-year period met enrollment criteria. Of these, 165 (68%) had desquamation of either the fingers or toes or both during the one-month period after onset of fever documented by either direct observation or parental history. Desquamation of the fingers only was noted in 44 subjects (26.6%), desquamation of the toes only in 8 subjects (4.8%), and desquamation of both in 107 subjects (64.8%). For 6 subjects (3.6%) the site of desquamation was not specified. Subjects with and without desquamation were similar with respect to age, gender, ethnicity, illness day, percentage neutrophils, hemoglobin z score (zHgb, hemoglobin value normalized for patient age), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), platelet count, and response to IVIG. Subjects with desquamation had a lower white blood cell count, but higher percentage bands, and higher plasma concentrations of alanine amino transferase (ALT) and γ glutamyl transpeptidase (GGT) (Table). Analysis of subjects with elevated ALT (>40 IU/L) and GGT (>37 IU/L) values revealed that desquamation rates were higher in this subgroup (elevated ALT: 87/154, [56.4%] vs. 22/70 [31.4%], p=0.0005 and GGT: 92/160 [57.5%] vs. 28 /76 [37.3%], p=0.004 for subjects with and without desquamation, respectively). Of the 5 standard clinical criteria for KD, only edema of the hands and feet or erythema of the palms and soles were more frequent among subjects with desquamation (Table). Patients without desquamation were significantly more likely to have aneurysms despite treatment with IVIG within the first 10 days after fever onset. In the multivariate model analyzing white blood cell count, percentage bands, ALT and GGT concentrations and coronary artery status, both percentage bands and coronary artery status were independent predictors of desquamation.

Discussion

In this retrospective review, only two-thirds of KD patients were documented to have periungual desquamation. Our observed rate of desquamation is lower than in four previously reported series that specifically mention desquamation separately from the other extremity changes. In these series, the rate of desquamation was 98%, 94%, 93%, 83%, in Japanese, U.S. mixed ethnic (2 studies), and Chinese populations, respectively(5-8). Although the original report by Kawasaki (1,2) had a very high rate of desquamation in Japanese KD patients, these patients received no effective anti-inflammatory therapy and were observed daily in the hospital. These factors may have influenced both the rate and the detection of periungual desquamation. Whether genetic factors may also have influenced the rate of desquamation is unknown. There was no evidence that ethnicity affected the incidence of desquamation in our series, although the number of subjects of Asian ancestry was small (14.8%). It is possible that uniform treatment of all patients in this study with IVIG at a dose of 2g/kg lowered the rate of desquamation as compared with the previously cited studies in which IVIG was either not used or its use was inconsistent. Our study used a lighted magnifying lens to detect desquamation and more cursory examination without magnification might have resulted in an even lower figure for the percentage of patients with peeling after acute KD.

Elevation of inflammatory markers (e.g. CRP and ESR) was not associated with desquamation, although an increased percentage of bands was an independent predictor of peeling. Subjects who did not peel were more likely to develop aneurysms, and this was confirmed in the

multivariate analysis. The association of elevated hepatic and hepatobiliary enzymes with desquamation was unanticipated. Although this association could be a spurious result of multiple comparisons or small sample size, the magnitude and congruent directionality of the association for both hepatic enzymes suggest that the observation may be real, although the mechanism is unclear.

Limitations of our study include the retrospective nature of the review and the different timing of visits during the first month after onset of fever. Determining the presence or absence of desquamation was dependent in some cases on parental history which might have had variable accuracy. Although desquamation may be difficult to detect in younger infants, the use of a lighted magnifying glass may have improved detection and we found no difference in the ages of subjects who did or did not desquamate. Only patients with complete KD or coronary artery abnormalities were included in our series so the incidence of desquamation among patients with incomplete clinical signs (<3 clinical criteria and normal echocardiograms) cannot be addressed.

Clinicians should be cautioned not to exclude the diagnosis of KD simply on the basis of the absence of desquamation. KD should be considered in the differential diagnosis in any child with prolonged, unexplained fever, regardless of the development of periungual desquamation in the convalescent phase.

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TABLE

Laboratory and clinical characteristics of Kawasaki disease patients with or without desquamation following the acute illness.

Characteristics	Desquamation (n = 165)	No desquamation (n = 78)	p value
White blood cell count (× 10^3 cell/mm^3)	13.1 (4.8 – 32.4)	15.3 (1.4 – 29.3)	0.009
Band Forms (%)	15.5 (0 – 65)	11 (0 – 49)	0.011
Alanine transaminase (U/L)	50 (5 – 1045)	27.5 (3 – 725)	0.0006
γ-glutamyl transpeptidase (U/L)	52.5 (2.3 432)	27 (6 427)	0.02
Coronary artery outcome, no.,(%)			0.022
Normal z-score <2.5	110 (67)	53 (68)	
Aneurysm	8 (5)	11 (14)	
Transient Dilation, z score ≥ 2.5	47 (28)	15 (19)	
Rash, no.,(%)	159 (96)	75 (96)	NS
Conjunctival injection, no.,(%)	152 (92)	71 (91)	NS
Oropharyngeal changes, no.,(%)	160 (97)	72 (92)	NS
Cervical lymphadenopathy, no.,(%)	38 (23)	27 (35)	0.053
Palm/sole erythema, edema of hands/feet, no.,(%)	142 (86)	52 (67)	0.0007

All values are medians (ranges) unless otherwise specified.