Case Clustering in Pityriasis Rosea

A Multicenter Epidemiologic Study in Primary Care Settings in Hong Kong

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Objectives: To investigate the epidemiology of pityriasis rosea in primary care settings in Hong Kong and to analyze for temporal clustering.

Design: Retrospective epidemiologic study.

Setting: Six primary care teaching practices affiliated with a university.

Patients: Forty-one patients with pityriasis rosea, 564 patients with atopic dermatitis (negative control condition), and 35 patients with scabies (positive control condition).

Methods: We retrieved all records of patients with pityriasis rosea, atopic dermatitis, or scabies diagnosed in 3 years. We analyzed temporal clustering by a method based on a regression model.

Results: The monthly incidence of pityriasis rosea is negatively but insignificantly correlated with mean air temperature ($\gamma_s = -0.41$, $P = .19$) and mean total rainfall ($\gamma_s = -0.34$, $P = .27$). Three statistically significant clusters with 7, 6, and 7 cases were identified ($P = .03$), occurring in the second coldest month in the year (February), the second hottest month (July), and a temperate month (April), respectively. For atopic dermatitis (negative control condition), the nonclustering regression model was selected by Akaike information criteria. For scabies (positive control condition), 1 cluster of 20 cases was detected ($P = .03$).

Conclusions: Significant temporal clustering independent of seasonal variation occurred in our series of patients with pityriasis rosea. This may be indicative of an infectious cause.

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The cause of pityriasis rosea (PR) is unknown. Drago et al\textsuperscript{1,2} reported the association of PR with human herpesvirus 7 infection. Other investigators, however, have described conflicting results.\textsuperscript{3-8} Our group previously reported the lack of evidence of active human herpesvirus 7 infection in children\textsuperscript{9} and adults\textsuperscript{10} with PR. We also reported the absence of active infection by Chlamydia pneumoniae, Chlamydia trachomatis, Legionella longbeachae, Legionella micdadei, Legionella pneumophila, and Mycoplasma pneumoniae in patients with PR.\textsuperscript{11}

However, evidence supporting an infectious cause of PR is still emerging. A double-blind placebo-controlled study\textsuperscript{12} reported benefit of erythromycin in modifying the course of PR. Ninety patients with PR were alternately assigned to treatment and placebo groups; 33 (73%) of the 45 patients in the treatment group achieved complete response after 2 weeks of treatment, while none did so in the control group ($P < .001$). There have been many case reports of 2 or more patients with PR in the same family or intimate environment.\textsuperscript{13-16} Epidemiologic studies reported associations of PR with history of respiratory tract infections\textsuperscript{17} and unfavorable social and economic background,\textsuperscript{18} and higher incidence among workers in larger collectives.\textsuperscript{19} McPherson et al\textsuperscript{20} reported that significantly more dermatologists than otolaryngologists had had PR, claiming that frequent exposure to PR by dermatologists during their practice led to an increased risk.

Cluster analysis is an epidemiologic approach to investigate a possible infectious cause and has been applied in diseases including childhood leukemia\textsuperscript{21} and Kawasaki disease.\textsuperscript{22} Only 1 study has investigated clustering in PR. Messenger et al\textsuperscript{23} in 1982 reported significant spatial-temporal clustering in female patients with PR in primary care settings, but not among male patients. They also adopted a “mov-
ing window” test and reported a temporal cluster of 16 cases within a 28-day period. It has been criticized that the degree of clustering found may not be valid to support an infectious hypothesis.24 No control was analyzed to establish the validity of their methodology. The effect of seasonal variation was not analyzed. Messenger et al suspected that the prospective nature of their study might have led to enthusiasm of participating general practitioners in reporting the cluster.23 Another prospective study in PR also found such reporting bias.25 In this regard, a retrospective study may paradoxically be better, as such reporting bias is absent.

Different approaches to test temporal clustering are possible. The test statistic of the cell-occupancy approach30 is the number of cases occurring in a subinterval. This method needs to divide the time period into disjointed subintervals arbitrarily. For the scan test,27 the test statistic, the maximum number of cases observed in an interval of a given length t, is found by scaling all intervals of length t in the time. For the scan test with a variable window,28 the cluster time window size does not need to be chosen a priori. This test only considers clusters with 5 or more events. With the rank-order procedure,29 the time is divided into subintervals. The test statistic is the sum of the absolute differences between the rank of the subinterval in which a case occurs and the median subinterval rank. This test is sensitive only to unimodal clustering and cannot distinguish between multiple clusters and randomness.

We report here a multicenter retrospective study conducted in primary care settings. Atopic dermatitis and scabies were analyzed concomitantly as control conditions. Atopic dermatitis was chosen as a negative control condition, as it is common, easily diagnosed by family physicians, and clearly known to be noninfectious (although it can be exacerbated by infections). Scabies was selected as a positive control condition, as it is common, easily diagnosed by family physicians, and clearly known to be infectious. Any valid methodology to analyze temporal clustering would be expected to identify nonclustering for the negative control condition and presence of clustering for the positive control condition. Climate data were also analyzed to evaluate the effect of seasonal variation.

The method used in our present study30 does not impose a division of the time. This approach determines time windows with excess events. For any position of the window, it scans continuously across the period of observation. The method is effective with multiple clusters, and the existence of 1 or more clusters is determined by using bootstrapped simulations, which allow us to increase the robustness of the test. The validity of this method has been established by applying it to the classic Knox data set13 and 62 spontaneous admissions for hemoptysis at Nice Hospital in Nice, France.32

The objectives of this study were to investigate the epidemiology of PR in primary care settings in Hong Kong and to analyze for temporal clustering.

**METHODS**

All affiliated primary care teaching practices with computerized record retrieval systems whose principals agreed to have their records searched were invited to participate. We searched with the strings pityriasis rosea, atopic dermatitis/atopic eczema, and scabies and retrieved all medical records with these entities from March 1, 1999, to February 28, 2002. The diagnoses were all made clinically by trainers or trainees in family medicine. All had undergone hospital-based training that included training in dermatology in a format accredited by the Hong Kong College of Family Physicians.

We included a diagnosis of PR for analysis only if 3 of the following 4 clinical features were clearly and legibly documented on the medical record: (1) herald patch, (2) peripheral collarette scaling, (3) mainly truncal and proximal limb distribution, and (4) orientation of lesions along lines of skin cleavage, parallel to the ribs, or in a Christmas tree or anti–Christmas tree pattern. This is based on a set of diagnostic criteria validated by Chuh33 that has been applied in other studies.10,11

We documented the date of first diagnosis for each patient with PR and for patients with atopic dermatitis and scabies. We obtained data for the monthly mean air temperature, mean total rainfall, and mean relative humidity for the period studied from the Hong Kong Observatory. We analyzed the data with the nonparametric Spearman rank-order correlation coefficient (γs). All P values were calculated 2-tailed.

We analyzed the extent of temporal clustering by a method based on a regression model.30 The approach is first based on a transdetermination of the data set to produce values corresponding to the time (the distance) between successive cases. Under the nonclustering hypothesis, these values can be estimated by a constant. On the contrary, a piecewise constant model improves the fitting. We applied the method to obtain several models with different numbers of clusters. Once the cluster bounds had been computed for each model, we selected the model with the smallest Akaiké information criteria34 value to determine the number of clusters. To avoid sample effects and to obtain a P value, we computed again the criteria on 1000 bootstrapped samples. The P value corresponds to the percentage of bootstrapped samples for which the cluster model is selected with the Akaiké information criteria against the nonclustering model.

**RESULTS**

Six affiliated teaching practices agreed to participate. We searched the medical records and identified 41 cases of PR with the recorded clinical features fulfilling the criteria. Also identified were 564 cases of atopic dermatitis and 35 cases of scabies.

Of the 41 patients with PR, 20 were male and 21 were female (male-female ratio, 1:1.05). Their age ranged from 5 to 54 years (mean age, 25.9 years). The monthly incidence was unrelated to air temperature (γs=−0.04, P=.91).

The monthly incidence of PR was negatively correlated with monthly mean air temperature (γs=−0.41), i.e., there were more cases of PR in the colder months. However, the correlation was insignificant (P=.19). Correlation with monthly mean total rainfall was also negative (γs=−0.34) but insignificant (P=.27). The monthly incidence was unrelated to monthly mean relative humidity (γs=−0.04, P=.91).

Three statistically significant clusters were identified for patients with PR. Figure 1 presents the distance between successive cases and the best piecewise constant regression function. A short mean time between successive events indicates a cluster. The statistical model with 3 clusters has a significant value (P=.03) compared with the nonclustering hypothesis. This model detected a cluster of 7 cases between February 4, 2000, and...

For the negative control condition of atopic dermatitis, the constant (nonclustering) regression model was selected by Akaike information criteria. For the positive control condition of scabies, 1 cluster of 20 cases was detected between January 30, 2002, and March 7, 2002 ($P = .03$) (Figure 2).

COMMENT

Using a regression model and applying the Akaike information criteria for selecting models, we identified 3 statistically significant temporal clusters in our series of patients with PR. Our results are compatible with the results of Messenger et al.23 We adopted a retrospective approach to eliminate reporting bias found in prospective studies.23,25 In addition, we supported the validity of our analysis by concomitant analysis of 2 control conditions, establishing the nonclustering model for atopic dermatitis (negative control condition) and identifying significant clustering for scabies (positive control condition). In contrast to the report by Messenger et al,23 which was criticized because the degree of clustering found was not valid to support an infectious hypothesis,24 our results should provide adequate evidence to establish temporal clustering in PR.

The age and sex distributions of our 41 patients with PR were similar to those in other epidemiologic studies on PR.18,23,25,35-43 Some studies23,37,39 reported higher incidence of PR in the colder months, one40 reported higher incidence in the early part of the rainy season, and some35,36,43 reported no seasonal variation.

### Epidemiologic Studies of Pityriasis Rosea

<table>
<thead>
<tr>
<th>Source</th>
<th>Location</th>
<th>No. of Patients With Pityriasis Rosea</th>
<th>Male-Female Ratio</th>
<th>Seasonal Variation</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vollum,35 1973</td>
<td>Uganda</td>
<td>221</td>
<td>1:1.22</td>
<td>Reported none</td>
<td>2.33/100 Dermatologic patients</td>
</tr>
<tr>
<td>Jacyk,36 1980</td>
<td>Nigeria</td>
<td>138</td>
<td>1:1.12</td>
<td>Reported none</td>
<td>2.42/100 Dermatologic patients</td>
</tr>
<tr>
<td>Messenger et al,23 1982</td>
<td>England</td>
<td>126</td>
<td>1:1.80</td>
<td>Higher incidence in winter months</td>
<td>Not reported</td>
</tr>
<tr>
<td>Chuang et al,37 1982</td>
<td>Rochester, Minn</td>
<td>939</td>
<td>1:1.76</td>
<td>Significantly higher in colder months</td>
<td>172.2/100 000 Person-years</td>
</tr>
<tr>
<td>de Souza Sittart et al,38 1984</td>
<td>Brazil</td>
<td>682</td>
<td>1:3.01</td>
<td>Higher incidence in June, October, and November</td>
<td>0.39/100 Dermatologic patients</td>
</tr>
<tr>
<td>Ahmed et al,39 1986</td>
<td>Sudan</td>
<td>81</td>
<td>1:1.53</td>
<td>Peaked in cold and dry season (January to March)</td>
<td>1.09/100 Dermatologic patients</td>
</tr>
<tr>
<td>Olumide et al,40 1987</td>
<td>Lagos</td>
<td>152</td>
<td>1:1.20</td>
<td>Peaked during early part of rainy season (March to July)</td>
<td>4.80/100 Dermatologic patients</td>
</tr>
<tr>
<td>Cheong and Wong,25 1989</td>
<td>Singapore</td>
<td>214</td>
<td>1.85:1</td>
<td>Higher incidence in March, April, and November</td>
<td>Not reported</td>
</tr>
<tr>
<td>Harman et al,41 1998</td>
<td>Eastern Anatolia</td>
<td>399</td>
<td>1:1.21</td>
<td>Peaked during spring, autumn, and winter</td>
<td>0.75/100 Dermatologic patients</td>
</tr>
<tr>
<td>Nanda et al,42 1999</td>
<td>Kuwait</td>
<td>117</td>
<td>1:1.38</td>
<td>Not reported</td>
<td>1.17/100 Dermatologic patients</td>
</tr>
<tr>
<td>Tay and Goh,43 1999</td>
<td>Singapore</td>
<td>366</td>
<td>1:19:1</td>
<td>Reported none</td>
<td>0.65/100 Dermatologic patients</td>
</tr>
<tr>
<td>Traore et al,44 2001</td>
<td>Burkina Faso</td>
<td>36</td>
<td>Not reported</td>
<td>Not reported</td>
<td>0.6/100 Secondary school children (prevalence in a cross-sectional survey)</td>
</tr>
</tbody>
</table>

Figure 1. Pityriasis rosea data transformation and 3-cluster regression function.

Figure 2. Scabies data transformation and 1-cluster regression function.
We found slightly higher incidence of PR in the colder months and months with less rainfall, although such correlations were weak and insignificant. Seasonal variation could have contributed to apparent temporal clustering. However, the 3 clusters of PR occurred in February 2000, July 2000, and April 2001. According to data from the Hong Kong Observatory, February is the second coldest month in the year, July is the second hottest month in the year, and April is a temperate month. The temporal clustering demonstrated is therefore highly likely to be genuine and independent of seasonal variation.

It has been postulated that PR may be due to reactivation of a latent virus rather than a primary viral infection. Is temporal clustering compatible with reactivation? We believe that it is. Varicella zoster is a typical viral reactivation disease. For unknown reasons, temporal clustering has also been demonstrated in that disease. We thus believe that further studies to investigate the question of primary infection or reactivation of pathogens are strongly warranted.

Our study has several limitations. Only a small number of patients with PR were identified during the study period. Underrecognition of this condition by primary care physicians might have been one important factor for this small number. We are unaware of any previously reported study on the epidemiology of PR in Hong Kong. We have tried to compare our number of patients with those of 2 epidemiology studies reported in Singapore. However, these 2 studies were performed in specialist settings, and a difference in the denominator renders direct comparison difficult. Another weakness is that the 6 participating practices were not randomly selected. Some selection bias could be present. Although a retrospective method does reduce reporting bias, some cases could have been missed.

Some patients may have visited a dermatologist instead of a primary care physician, and this may also contribute to the small number of patients. We elected to conduct this study in primary care settings rather than in specialist dermatology centers, as we believe that primary care morbidity is the closest proxy measure of a community diagnosis. Care in specialist settings cannot truly reflect the epidemiologic picture in the community. We opted to analyze the dates of first diagnosis rather than the estimated dates of rash onset, as many patients could have missed the herald patch (if any) or could not be definite about the rash onset date.

Epidemiologic data represent only one of several elements of factors supporting the association of PR and an infectious cause. We believe that such association is far from fulfilling Hill’s causality criteria—namely, strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experimental evidence, and analogy. However, as the epidemiologic evidence favors an infectious cause, further laboratory investigations to look for the underlying pathogen are strongly indicated.

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REFERENCES


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