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Review Article

A qualitative study on the historical aspects of pityriasis rosea: revelations on future directions of research

玫瑰糠疹歷史的簡要研究：對未來研究方向的啟發

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The exact aetiology of pityriasis rosea (PR) remains controversial despite research for nearly one and a half century. We report a small-scale qualitative study on the historical aspects of PR. We found that the exact time point for which the rash was first accurately described is not easily determined. There exists considerable overlap between typical and atypical PR. Important clinical signs of PR such as the herald patch and peripheral collarette scaling were recognised decades after the disease had been accurately described. Early investigators utilised not only laboratory data but also epidemiological data in their analyses. Investigators often focused on physician-oriented rather than patient-oriented aspects. These findings have pertinent implications on the future directions of research for PR.

雖然經過了近一個半世紀的研究，我們對玫瑰糠疹的確實致病原因仍未定案。我們　述了一項有關玫瑰糠疹歷史的簡要研究。我們發現了玫瑰糠疹精確的首次描述時期不易肯定，而典型及非典型的病例非常重疊；前驅班及外周圍巾性脱屑等重要的臨牀徵狀，都是在此病症描述了數十年後才被發現的。初期的研究者除了用化驗數據外，也用流行病學數據來作分析；研究者多集中於醫生關注的事項，而非患者關注的事項。這些發現對玫瑰糠疹未來的研究方向有着重要的啟發作用。

Keywords: Diagnostic criteria, human herpesvirus 7, pityriasis rosea, quality of life

關鍵詞：斷症標準，人類疱疹病毒 7 型，玫瑰糠疹，生活質素

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Background

Despite research by generations of investigators for near one and a half century, the exact aetiology of pityriasis rosea (PR) remains a debatable issue. We have previously reported that PR is not associated with infections by human herpesvirus (HHV)-6, HHV-7,[1,2] cytomegalovirus, Epstein-Barr virus, parvovirus B19,[3] *Chlamydia pneumoniae, C. trachomatis, Legionella longbeachae, L. micdadei, L. pneumophila,* and *Mycoplasma pneumoniae*.[4] We proposed and validated a set of diagnostic criteria,[5] reported significant temporal clustering,[6,7] and quantified the effects of PR on quality of life of patients.[8,9] A study on the association of PR with HHV-8 infection is in progress.[10] A Cochrane review on the effectiveness and safety of interventions in PR is also in progress.[11]

Should further efforts be put to demystify the final culprit in PR? Does the elucidation of the cause in PR incur direct bearings on its management? What should be the future focuses of research for this intriguing exanthem? We report here a small-scale qualitative study on the historical aspects of PR, and discuss its revelations to the aforementioned queries.

Methods

We searched Medline with the entrez *pityriasis rosea, Gibert,* and *historical* using various Boolean operators, and retrieved all articles related to historical aspects of PR. We scanned the bibliographies for possible references to older articles published since PR was first described.

We then requested for the assistance of the Rare Books Librarian, Library of the Royal College of Physicians of Edinburgh, and the College Librarian, Historical Collection, Library of the Royal College of Physicians and Surgeons of Glasgow, for further searching and retrieving information on the historical aspects of PR. We requested the Société Française d'Histoire de la Dermatologie to retrieve relevant historical images. We also contacted the Department of Dermatology, University of Edinburgh, for assistance in retrieving historical pictures.

Results

Twenty-eight references[12-39] were retrieved and reviewed. We summarise hereby the historical aspects of PR along a chronological order of events.

Robert Willan and description of the eruption before 1860

According to our search results, the term pityriasis was first coined by the great Greek physician Claudius Galen (AD129-216) to describe dandruff.[12] Robert Willan (1757-1812), an Edinburgh graduate, was regarded by many as the father of modern dermatology. He devised the first modern classification of skin diseases. Psoriasis was once termed *Willan's lepra* or *Willan's syndrome*. Willan adopted the term pityriasis to describe four varieties of scaly skin rashes, namely *pityriasis capitis, pityriasis rubra, pityriasis versicolor* and *pityriasis nigra*.

We found that Willan subsequently described a rash, which he termed *roseola annulata* in 1798. Pierre François Olive Rayer (1793-1867), a French dermatologist, described a very similar rash termed *erythema annulatum* in 1828.[12] Erasmus Wilson (1809-1884), the first professor of dermatology at London University, wrote about *lichen annulatus serpinginosus* in 1857. He described *small, flat, erythematous discs, bounded by a sharp and distinct margin... and converted into rings*.[13] It is believed that these rashes were in essence what would be named *pityriasis rosea* later.[13]

Camille Melchior Gibert and pityriasis rosea

Camille Melchior Gibert (1797-1866) (Figure 1) – a professor at the Medical College of Paris, and later served in Hôpital Saint-Louis (Figure 2) – was

generally given the credit for the first accurate description of the rash[12,14,15] and for introducing the term pityriasis rosea.[16] Since his description of the definite course of the condition, PR was generally recognised as a distinct clinical entity.[12]

According to *Dictionnaire Encyclopédique des Sciences Médicales* (1882), PR was first described by Professor Gibert in 1860, on page 402, volume one of the third edition of *Traité pratique des maladies de la peau*.[17] Gibert described five varieties of *pityriasis: pityriasis simple, pityriasis rosea, pityriasis rubra, pityriasis versicolor,* and *pityriasis nigra*. He considered PR to be an intermediate variety between *pityriasis simplex* and *pityriasis rubra*,[18] and clearly separated PR from psoriasis and scaling secondary syphilis.[19] He made a statement that PR is *subject to recurrences*. He remarked that repeated experiments failed to show any fungus in PR.

Figure 1. Camille Melchoir Gibert (1797-1866), who first introduced the term *pityriasis rosea* in 1860. (Reproduced with permission from Daniel Wallach, MD, Société Française d'Histoire de la Dermatologie)

Pierre-Antoine-Ernest Bazin and annular pityriasis rosea

Our search results clarify that Gibert only described the macular variety of PR, not the usual annular variety. The latter was first described by Pierre Antoine Ernest Bazin (1807-1878) (Figure 3) in 1862.[18] Bazin also made the earliest remark on

Figure 3. Pierre Antoine Ernest Bazin (1807-1878), who first described annular pityriasis rosea in 1862, and made the earliest remark on prodromal malaise in pityriasis rosea. (Reproduced with permission from Daniel Wallach, MD, Société Française d'Histoire de la Dermatologie)

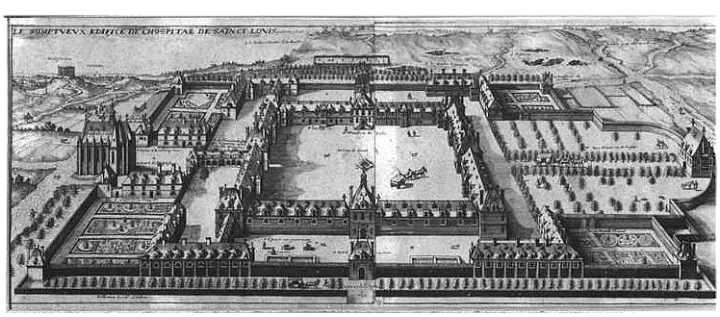

Figure 2. Hôpital Saint-Louis. Gibert first described the macular variety of pityriasis rosea in this hospital in 1860. Bazin subsequently described the annular variety here in 1862. Vidal described pityriasis circiné et marginé also in this hospital in 1882. Brocq, head of the medical department of this hospital from 1906-1921, first described the *plaque primitive* or the *primitive patch* in 1887. (Reproduced with permission from Daniel Wallach, MD, Société Française d'Histoire de la Dermatologie)

prodromal malaise in PR.[12] Bazin studied in Paris and later served in Hôpital Saint-Louis in 1847 where developed his interests in dermatology. Bazin is most famous for his original description of *Bazin's disease* (erythema induratum), one of the cutaneous manifestations of tuberculosis.

Pityriasis circinata et marginata of Vidal and other synonyms

Jean Baptiste Emile Vidal (1825-1893) (Figure 4), another French dermatologist, described a similar condition which he termed *pityriasis circiné et marginé*, also in Hôpital Saint-Louis, in 1882.[18]

Vidal was familiar with PR and had already written on PR when he described *pityriasis circiné et marginé*. He was of the opinion that PR and *pityriasis circiné et marginé* were different conditions as the latter run a longer course of about six months. Vidal claimed that he had discovered bodies in the scales of the latter condition, which he named *Microsporon anomoeon*.[12]

Some dermatologists considered *pityriasis circinata et marginata of Vidal* a special form of PR, with fewer and larger lesions often localised at the axillae or groins.[18,20,21] Other dermatologists maintained that *pityriasis circinata* and *pityriasis circinata* et marginata should be synonyms of PR.[12] Other synonyms of PR are of historical interests only, and include *herpes tonsurans maculosus* (described by Hebra in 1876),[22] *pityriasis disséminé* (described by Hardy in 1868),[22] *pityriasis rubra aigu, roseole squameuse of Chapard* and *pityriasis maculata et circinata of Bazin*. It should be noted that *Vidal's disease* and *Vidal's syndrome*, both named after Jean Baptiste Emile Vidal, are synonyms of lichen simplex chronicus, totally unrelated to PR.

First descriptions of herald patch and peripheral scaling

It was Louis Anne Jean Brocq (1856-1928) (Figure 5), also a dermatologist in Hôpital Saint-Louis and head of the medical department from 1906-1921, who drew attention to the *plaque primitive* or *primitive patch* as a distinctive diagnostic sign in 1887, 27 years after Gibert's description of PR.[13]

In 1899, Alfred Blaschko (1858-1922), a German dermatologist, famous for his description of *Blaschko's lines*, pointed out that *in PR there is exfoliation from the centre to the periphery, while*

Figure 4. Jean Baptiste Emile Vidal (1825-1893), who described *pityriasis circiné et marginé* in 1882. Vidal claimed that he had discovered bodies in the scales from these patients, which he named *Microsporon anomoeon*. (Reproduced with permission from Daniel Wallach, MD, Société Française d'Histoire de la Dermatologie)

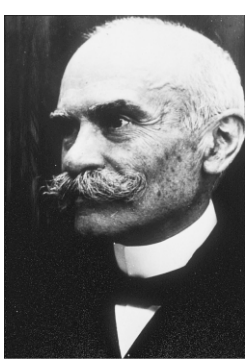

Figure 5. Louis Anne Jean Brocq (1856-1928), who drew attention to the *plaque primitive* or *primitive patch* as a distinctive diagnostic sign in 1887, 27 years after Gibert's description of PR. (Reproduced with permission from Daniel Wallach, MD, Société Française d'Histoire de la Dermatologie)

in psoriasis desquamation takes place from the periphery to the centre.[13]

First reports coining pityriasis rosea in the American and British medical literature

Louis Dühring presented six cases of PR in the fourth annual meeting of the American Dermatological Association in 1880. He is considered to be the first American to describe the eruption.[13]

Alan Jamieson, who started the first outpatient dermatology clinic in Edinburgh in 1884, first reported PR in the *Edinburgh Medical Journal* in 1881, and subsequently in the *British Medical Journal* in 1882.[12] He believed that PR was *a new dermatomycosis which approaches nearer to pityriasis versicolor than to tinea tonsurans*.[23] Colcott Fox subsequently reported five cases of PR in children in 1884. PR was first described in British medical textbooks in 1888.[12]

Reports of pityriasis rosea around the world

The earlier epidemiology studies were mainly reported in France and in the United Kingdom.[12] It was soon realised that susceptibility to PR differs little across different races. The more recent epidemiology studies were reported, in chronological order, in the United Kingdom,[24-26] Uganda,[27] Nigeria,[21] United Kingdom again,[28] Rochester in Minnesota,[16] Brasil,[29] Sudan,[30] Lagos,[31] Singapore,[32] Turkey,[33] Kuwait,[34] Singapore again,[35] and in Burkina Faso.[36]

Interesting early studies to identify the aetiology

Early experiments have been reported to attempt to transmit PR or to treat PR with convalescent plasma. These studies worth being covered here as they might probably never be repeatable on human subjects owing to modern ethical standards.

One investigator obtained the blister contents of primary and secondary lesions in PR.[37] Bacterial cultures from the contents were negative. He injected the contents percutaneously into the skin of volunteers. An aberrant form of PR was seen, characterised by fulminant appearance of disseminated papules in the characteristic distribution with a shorter clinical course.

Investigators have also given pooled immunoglobulin[38] or convalescent sera[39] to patients with PR. These patients were reported to have a shorter duration of the disease.

Early classification

A scheme has been proposed for classifying the usual and unusual varieties of PR.[18] This classification was along two axes: rash morphology and rash distribution. Rash morphological divisions were macular (subclassified into punctate, guttate, nummular and circinate), urticarial (*PR urticata of Vorner and urtiée PR of Hallopeau*), papular (maculopapular, follicular, large miliary, small miliary), and vesicular. Rash distribution divisions were bilateral, unilateral, generalised, localised, and confluent and diffuse (subclassified into *PR gigantean of Darier and pityriasis circiné et marginé of Vidal*).

Modern nomenclature and classification

Pityriasis rosea was coded 696.3 in the International Classification of Diseases (ICD), Ninth Revision, Clinical Modification. It was listed under 696, *Psoriasis and similar disorders*. *Pityriasis circinata (et maculata)* was listed as a synonym of PR under code 696.3. There was no entry for *pityriasis rosea due to drug*.

In ICD-10, *pityriasis rosea* is coded L42X00. *Pityriasis rosea due to drug* is coded L44X01, signifying that PR-like rash related to drugs is now considered a distinct condition. *Gibert's disease, pityriasis circinata* and *pityriasis circinata et marginata of Vidal* are all also coded L42X00, denoting that they are synonyms of PR. The atypical forms of PR are not formally listed in the classification system.

Discussion

We earned pertinent observations from reviewing the historical aspects of PR. Firstly, the pivotal moment for which the rash was first accurately described is controversial. We might never be able to ascertain whether *roseola annulata* described by Willan, *erythema annulatum* described by Rayer, and *lichen annulatus serpinginosus* as described by Wilson were PR, variants of PR, or indeed a constellation of several dermatoses. We have contacted various sources. However, we have not been able to retrieve images of these early descriptions of PR. While we cannot doubt the contribution of Gibert for the original description and nomenclature, and for establishing PR as a distinct clinical entity, he described only the macular variety of PR, not the more usual annular configuration. We realise that such might not be related to real morphological differences. Instead, investigators may use slightly different terms to describe the same lesions. Moreover, the morphology of lesions might change in the course of the disease.

The connotation of such finding is that there are always grey zones in the descriptions of clinical signs of diseases particularly skin diseases. Diagnostic criteria has been proposed and validated for common skin diseases such as atopic dermatitis.[40] Such allows studies on atopic dermatitis from investigators around the world to be validly compared with each other. It was definitely immature for Gibert or even Vidal to establish a set of diagnostic criteria. However, in view of proliferation of studies on the viral aetiology and active interventions for PR in the recent decade, it might be the appropriate moment for us to consider a universal adoption for the diagnostic criteria.

The second finding is that the distinction of typical and atypical PR is a grossly oversimplified picture, and has never been a straightforward task. The status of entities such as drug induced PR and *pityriasis circiné et marginé* has been controversial until fairly recently.

This finding is vital in the valid interpretation of clinical trials on patients with PR. As an example, we have found that while one randomised clinical trial on PR included patients with atypical PR,[41] another randomised clinical trial explicitly excluded all patients with atypical PR.[42] Several randomised clinical trials did not explicitly exclude patients with drug-induced PR-like rash.[41-43] Such incongruence in the inclusion and exclusion criteria convolutes the conduction of systematic reviews and meta-analyses, and confines the generalisability of findings to clinical practice.

The third discovery is that important clinical signs, which we now consider to be the signature manifestations of a condition, might be recognised decades after the disease has been accurately described and named. The herald patch was first described 27 years after the nomenclature of PR.[13] The direction of scaling which gives rise to the characteristic peripheral collarette scaling configuration was described 39 years after the original nomenclature.[13]

The pertinence is that we should not concentrate our research on high profile technological aspects alone, but should also save ample time and energy to study the clinical features visible to our naked eyes. There exists every possibility that important symptoms and signs have not been described for relatively common diseases and rashes.

The fourth finding is that while PR has long been suspected to have an infectious aetiology, early investigators have been employing not only laboratory data but also epidemiological data in their analyses. Apart from temporal clustering in PR,[28] there have been case reports of two or more patients with PR in the same family or intimate environment.[44] For example, PR was reported to occur in two sisters separated by a period of six

weeks,[45] and another pair of sisters with successive onset of PR 61 days apart.[46] A 60-year-old farmer was reported to have PR, followed by PR occurring in his 30-year-old daughter three months later.[47] A mini-epidemic of PR has also been reported. In a whaling ship trip to the Antarctic, four cases of PR were reported to occur within one month.[48] The authors argued that as the whaling ship was a closed community, such occurrence supported an infectious aetiology. The deliberation is that we should make decent use of epidemiological data to supplement laboratory results in investigating the infectious aetiology of PR.

Lastly, we found that as with many other conditions, investigators often focus themselves on physician-oriented aspects of the disease rather than patient-oriented aspects. It has only been fairly recently that investigators documented how PR is perceived by patients, how PR affects their quality of life, and what concerns parents of children with PR have. PR is essentially a self-limiting exanthem. Only about 50% of all patients endure pruritus of moderate to severe intensity. For many patients, PR does not bother them apart from a peculiar diagnostic label in Latin. Any active intervention, even if convincingly proven to be of efficacy in modifying the course of events, might not be warranted if patients do not expect active intervention in the first place. Adverse reactions have to be balanced against their efficacies, and the formers have not been given adequate attention in many of the historical clinical reports and even some clinical trials conducted fairly recently.

Upon completing this small-scale study, we believe that further efforts should be made to unveil the final culprit in PR, not for academic interests alone but also for direct impacts on patient reassurance and management. We envisage that future directions of research should be to establish the validity, reliability, and applicability of a diagnostic criteria, to use epidemiological data to complement laboratory data in elucidating the aetiology, and to use patient-oriented outcomes such as pruritus and effects on quality of life in addition to traditional physician-oriented outcomes such as rash extensiveness in randomised controlled trials and systematic reviews.

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