THE SPARING PHENOMENON. A CASE SERIES OF THE INVERSE KOEBNER AND RELATED PHENOMENA

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Abstract

Introduction: The sparing of the involvement of a cutaneous disease in a site that has been previously subjected to a skin disease, congenital nevus or physical insult has been reported in literature by various names, including the inverse Koebner phenomenon.

Objectives: To review cases that we have seen and to document the reported cases and unify them with a single term, the “Sparing phenomenon”.

Materials and Methods: We report four new examples of this phenomenon and performed a PubMed literature search on related search terms and summarized the reported cases.

Results: We report four new cases of this phenomenon. An additional 16 reported cases of the sparing phenomenon were identified. Herpes zoster was the most reported inflammatory disease site followed by; skin irradiation was the commonly documented physical insult. Drug reactions and psoriasis were the most common diseases that spare these sites. The time gap between first and second insult was highly variable.

Conclusions: We proposed the term “Sparing phenomenon” to describe the skin disease sparing on an area which was previously subjected to skin disease or physical insult. By introducing this new term to the dermatology glossary, it would be easy to collect and analysis to understand the immuno-pathophysiology of this skin reaction described in various names.

Key words: phenomenon; koebner phenomenon; inverse koebner phenomenon

Introduction

In 1876 the German physician Heinrich Koebner described a characteristic phenomenon in a psoriasis patient who had been bitten by a horse and developed new psoriatic lesion at the site of trauma [1]. Subsequently this skin reaction, which has been documented in various other skin diseases, was named as the “Koebner phenomenon”, “Isomorphic response” or “Isomorphic phenomenon”.

In contrast to this well-known observation in which skin disease is produced in the site of trauma, infrequently disease may be spared in the site of trauma. Cochran and colleagues in 1981 first described a macular papular drug reaction which spared the sites of previous X-irradiation in a patient with had been treated for Wilm’s tumor [2]. Bernhard et al later introduced the term “Koebner non reaction” or “Isomorphic nonresponse” to refer the absence of a drug reaction at the site of the previous x-irradiation [3]. A variety of other related observations have also been reported. The Renbok Phenomenon or “Inverse Koebner Phenomenon” was described as normal hair growth in psoriatic patches noted in patient with co-occurrence of psoriasis and alopecia areata [4-7].

In 1995 Wolf et al introduced “Isotopic nonresponse” to describe the absence of an eruption at the site of another, unrelated, and already healed skin disease in their article of “Isotopic response” [8].

We propose to unify these disparate observations and terms under the rubric, “The Sparing phenomenon”. In brief, the sparing phenomenon refers to absence of manifesting a particular skin disease on an area previously affected by another skin disease and physical or chemical insult (e.g., U.V or X-Irradiation).

Methods

We present 4 cases that fit the criteria of Sparing phenomenon seen in our clinics from 2003 to 2006. A comprehensive PubMed literature review was performed. Search terms included “Koebner nonreaction”, “Inverse Koebnerization”, “Isomorphic nonreaction”, and „Renbock phenomenon”.

Cite this article:

The reference sections of articles obtained were also searched for relevant articles.

**Results**

**Case Series:**
The demographics and presentation of four are included in Table I which summarizes the clinical presentation, the diseases involved, the time interval between two diseases and the affected site of our patient’s diseases. Three cases related to previous herpes zoster site and one case on an area previously affected by contact dermatitis were spared by cutaneous t-cell lymphoma (CTCL), Stevens-Johnson syndrome/Toxic epidermal necrolysis (SJS-TEN) and rubber slipper dermatitis (Fig. 1, 2).

**Literature Review and Summary:**
All the cases reported under the specific name such as “Koebner non-reaction”, “Inverse Koebner phenomenon”, “Isomorphic non response” and “Renbok phenomenon” are presented in Table II. Failure of a drug eruption to occur in a site that had undergone irradiation was the first documented sparing reaction in the literature [2]. Since then, non-existence of various forms of drug reactions in an areas previously subjected to an insult has been reported. Ampicillin and clotrimazol-trimethopim were the most noted culprits [2,3,9]. An area subjected to herpes zoster was the often resistant site for the many diseases including leprosy and CTCL [10-13]. Psoriasis sparring an area of alopecia areata and previously irradiated site was found in three occasions and non occurrence of drug reaction and CTCL in an area exposed to ultra violet light (swimming suit sparing) were documented in two instances [3-5,14,15]. There were two occasions granulomatous skin diseases sparing previous scar tissues [16,17].

There did not seem to be any association between first and second disease, the time gap between two insults were few weeks to 20 years. The most commonly involved area was face and scalp followed by chest and abdomen. Interestingly the left side of the body presented with the “Sparing phenomenon” more often right, unless previous injury was irradiation.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age &amp; Sex</th>
<th>First disease</th>
<th>Interval between first and second disease</th>
<th>Second disease</th>
<th>Site involved (Sparingsite)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>84 Female</td>
<td>Herpes zoster</td>
<td>4 months</td>
<td>Cutaneous t cell lymphoma</td>
<td>Left lower abdomen</td>
</tr>
<tr>
<td>2</td>
<td>57 Male</td>
<td>Contactdermatitis</td>
<td>3 months</td>
<td>Phyto-Photodermatitis</td>
<td>Feet</td>
</tr>
<tr>
<td>3</td>
<td>62 Male</td>
<td>Herpes zoster</td>
<td>3 months</td>
<td>Cutaneous t cell lymphoma</td>
<td>Left upper arm</td>
</tr>
<tr>
<td>4</td>
<td>53 Female</td>
<td>Herpes zoster</td>
<td>2 months</td>
<td>SJS-TEN</td>
<td>Left face</td>
</tr>
</tbody>
</table>

Table I. “Sparing phenomenon” cases seen at our hospitals

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![Figure 1. SJS/TEN sparing previous Herpes Zoster area](image1)

![Figure 2. CTCL sparing previous Herpes Zoster area](image2)

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<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age and Sex</th>
<th>Previous disease/ Congenital nevus/ Physical insult</th>
<th>Interval</th>
<th>Second disease</th>
<th>Site involved (Sparing site)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Cochran et al 1981</td>
<td>12 Female</td>
<td>Radiation for Wilm’s tumor</td>
<td>6 years</td>
<td>Drug reaction</td>
<td>Right side abdomen/ back</td>
</tr>
<tr>
<td>2. Bernhard et al 1982</td>
<td>26 Female</td>
<td>Radiation for liver secondary of Adenocarcinoma of unknown origin</td>
<td>Few days</td>
<td>Drug reaction</td>
<td>Right side abdomen</td>
</tr>
<tr>
<td>3. Bernhard et al 1982</td>
<td>Female</td>
<td>Ultraviolet light exposure</td>
<td>Few days</td>
<td>Drug reaction</td>
<td>Uncovered area of bathing suit</td>
</tr>
<tr>
<td>4. Pavitran 1987</td>
<td>Middle age Female</td>
<td>Tuberculoid leprosy</td>
<td>-</td>
<td>Drug reaction</td>
<td>Face</td>
</tr>
<tr>
<td>5. Katayama et al 1990</td>
<td>63 Male</td>
<td>Herpes zoster</td>
<td>4 weeks</td>
<td>Contact dermatitis</td>
<td>Left side abdomen</td>
</tr>
<tr>
<td>7. Huilgol et al 1995</td>
<td>74 Female</td>
<td>Vaccination scar</td>
<td>-</td>
<td>Generalized Granuloma annulare (+Multiple myeloma/Leukaemia)</td>
<td>Left upper arm</td>
</tr>
<tr>
<td>8. Ozkaya-Bayazit et al 1999</td>
<td>72 male</td>
<td>Burn scar</td>
<td>-</td>
<td>Annular elastocytic giant cell granuloma</td>
<td>Left forearm</td>
</tr>
<tr>
<td>9. Grilli et al 2002</td>
<td>72 Female</td>
<td>Ultraviolet light exposure</td>
<td>-</td>
<td>Mycosis fungoides</td>
<td>Uncovered areas of summing suit</td>
</tr>
<tr>
<td>10. Rosina et al 2003</td>
<td>18 Female</td>
<td>Alopecia areata</td>
<td>-</td>
<td>Psoriasis</td>
<td>Scalp</td>
</tr>
<tr>
<td>11, 12 Jain R et al 1993</td>
<td>Two patients</td>
<td>Herpes zoster</td>
<td>-</td>
<td>Borderline leprosy</td>
<td>-</td>
</tr>
<tr>
<td>13. Twersky et al 2004</td>
<td>58 Male</td>
<td>Herpes zoster</td>
<td>3 weeks</td>
<td>Cutaneous t cell lymphoma</td>
<td>Left side abdomen</td>
</tr>
<tr>
<td>14. Nikkels et al 2004</td>
<td>32 Female</td>
<td>Herpes zoster</td>
<td>Few days</td>
<td>Contact dermatitis</td>
<td>Left side abdomen</td>
</tr>
<tr>
<td>15. Martin et al 2006</td>
<td>53 Female</td>
<td>Radiation for intraductal carcinoma of breast</td>
<td>-</td>
<td>Psoriasis</td>
<td>Right breast</td>
</tr>
<tr>
<td>16. Cardio et al 2007</td>
<td>39 Female</td>
<td>Alopecia areata (Ophiasis)</td>
<td>20 years</td>
<td>Psoriasis</td>
<td>Scalp</td>
</tr>
</tbody>
</table>

**Table II. Reported cases related to “Sparing Phenomenon”**

**Discussion**

Two out of four of our hospital’s cases of sparing phenomenon that to our knowledge have not been described in the previous literature such as S.I.S -T.E.N sparing the area initially subjected to herpes zoster and strap marks of rubber slipper dermatitis are unaffected by phyto-photodermatitis. Three patients who spared the previous herpes zoster affected area also showed left side predilection. The term Renbok phenomenon or “Inverse Koebner phenomenon” (Happle et al in 1991) applies to normal hair growth in psoriatic patches noted in patient with both psoriasis and alopecia areata. In 1995 Wolf et al introduced “Isotopic nonresponse” to describe the absence of an eruption at the site of another, unrelated, and already healed skin disease in their article of “Isotopic response”. Because of very little evidence available in the literature as well as similarities between most reported cases of this unique entity we decided to broaden the definition of Sparing Phenomenon, rather than narrowing primary insult only to a skin disease.
When we have a better understanding about the Immuno-Patho-Physiology of this skin reaction, it would be easy to classify homogenous cases together for academic purposes in future. Possible hypotheses for pathophysiology of this phenomenon are:

1. The structural changes (cellular, vascular, neural) caused by first insult prevent the occurrence of second disease at the same site.
2. Changes of the microenvironment (immune and cytokines pathways) in the affected site caused by first injury leads to resistant to subsequent disease at the same site.
3. Combination of both reasons.

The exact pathophysiology of the skin disease sparing the previous skin insult has not been identified clearly, but several possible mechanisms which were described in the literature can be classified under the following headings.

Cellular Alterations:
Langerhans cells play an important major role in allergic contact dermatitis, drug reactions and epidermotropism in CTCL. Irradiation has been reported to induce loss of Langerhans cell and other immunological changes in the subjected skin [18]. Reduction of Langerhans cell number and it’s activity in herpes zoster lesion and their peripheral area has recently been documented by Katayama et al and Nikkles et al. [10,12,13]. This abnormality in Langerhans cell number could influenced drug reaction, allergic contact dermatitis and CTCL didn’t occur in the area affected by irradiation and herpes zoster.

Vascular Component Alterations:
The effect of ionizing radiation on cutaneous blood vessels that resulted in a reduced activity of blood vessels wall, a diminished vascular bed and reduced carriage of constitute agents to the affected site, and there by none existing of drug rash over the radiation portal was explained by Cochran and Bernhart et al. [2].

Cytokines Alterations:
Radiation treatment induced cytokines imbalance prevent the over expression of Type I pro-inflammatory cytokines which are commonly considered to be responsible for initiation, maintenance and recurrences of psoriasis were explained by Martin et al. [14]. Psoriasis lesion induced microenvironment which is rich in TNF-alfa is not a favorable environment for inflammation seen in alopecia areata was postulated by Hofman, Happle and several others [7].

Role of Intercellular Adhesion Molecule 1(ICAM-1):
Interaction of the ligand/receptor pair Lymphocyte Function Antigen 1 (LFA-1) and ICAM-1 initiate and control the cell-cell interactions of leucocytes with parenchymal cells in all stages of immune reaction. It has been shown that ultraviolet radiation leads to suppression of ICAM-1 on the surface of cultured human keratinocytes at 24 hours [19]. Thus prolonged repeated continuous ultraviolet radiation might have ability to suppress the ICAM-1 for long period of time. Keratinocytes of patients with lepromatous leprosy lesions were found to lacking in the ICAM-1 expression and the down regulation of ICAM-1 on herpes zoster virus infected keratinocytes are well documented entities in recent literature [13,20,21]. Hence the reduction or inhibition of ICAM-1 induction on keratinocytes by ultraviolet radiation, lepromatous leprosy or herpes zoster virus probably disables the keratinocytes to function as accessory antigen presenting cells and inhibits its role in LFA-1/ICAM-1 Mediated T cell response, and there by prevent the appearance of drug reaction and CTCL on previous skin insult.

Conclusion
By defining new term, “Sparing phenomenon” for already existing entity in different names, we believe that it is easy to locate and collect similar cases under a one key ward, to better understanding the Immuno-patho-physiology of this unique skin reaction as well as use of this mechanism as a therapeutic intervention for most serious skin disease like CTCL and SJS-TEN.

REFERENCES