False-Positive "Poral" Cobalt Patch Test Reactions Reside in the Eccrine Acrosyringium

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Seventy (32%) of 222 patients patch tested in our contact dermatitis clinic from 1993 to 1995 had irritant reactions to cobalt. These reactions were "poral" and seemed to reflect a unique and probably toxic effect of cobalt on the acrosyringium. The reactions are neither follicular nor petechial and we believe they are not allergic. The histopathology of the reactions is described in detail.

Patch-testing to metals can be confusing. Pustular reactions to metals have been appreciated and discussed by Alexander Fisher and his colleagues for some time. In the discussion of the 1959 paper by Fisher and colleagues,[2] Epstein mentioned that he had observed petechial reactions when testing with 10% cobalt nitrate, but only in atopics. Etain Cronin[3] noted that cobalt salts are mild irritants and may be associated with patch-test reactions characterized by "a punctate erythema which may become purpuric." Cronin[3] further noted that, "this speckled reaction is probably follicular" but ... "it is easily discernible from an allergic response."

The "petechial" reaction at cobalt patch test sites was studied by Schmidt *et al.*,[4] who found "petechial" cobalt reactions in 3 to 8.4% of the patients they tested. They biopsied five patients and observed dilated subpapillary capillaries with swollen endothelia and a slight lymphocytic infiltrate. The epidermis was not described, nor were adnexal structures. Extravasated erythrocytes were described, but not seen in the one photomicrograph that they included in their article.

From 1983 to 1985, Rystedt *et al.*,[5] and Fischer and Rystedt[6] published observations concerning 853 hard metal manufacturers. They reported irritant pustular reactions to sodium tungstate in 2% of these workers whom they biopsied nine times. They described "porite (follicular)" lesions that started juxtafollicularly and terminated in intrafollicular neutrophil-filled abscesses.[5]

In the 1985 paper describing these workers, Fischer and Rystedt[6] discussed nickel, chromate, and cobalt patch-test reactions. These reactions were not biopsied, but were read as allergic, irritant, pustular, or "follicular." The follicular reactions were called "poral" and were said to consist of "punctate erythema, sometimes slightly papular and/or hemorrhagic around the hair follicle openings, presenting as small dots irregularly distributed within the test area."[6] The authors assumed that these reactions were follicular, probably based on their biopsy experience with sodium tungstate patch-test reactions. "Poral" reactions occurred at nickel, chrome, and cobalt sites, but were most frequent at cobalt sites and were most likely to recur at cobalt-retested sites with diluted materials. Furthermore, and most importantly, when the testing materials were diluted, the 62 patients initially interpreted to be allergic to cobalt decreased to 39; 48 allergic to nickel decreased to 40; and 25 allergic to chrome decreased to 10. Clearly, the difficulty in evaluating cobalt and chrome reactions was demonstrated. The false-positive "poral" reactions, especially with cobalt, can lead to initial misinterpretations of allergy, which occasionally require dilutional testing for clarification and may actually not be so "easily discernible" from allergic reactions.

Appreciating these false-positive reactions allows for better interpretations of patient patch-test reactions and evaluation of scientific studies. Some studies of metal salts make no mention of probable cobalt irritant ("poral") reactions, which casts some doubt on their results.[7,8] Other studies cite a prevalence of 23% "questionable or irritant" reactions as opposed to 4.6% probable allergic cobalt reactions.[9] A preva-

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FIGURE 1. A 48-hour false-positive cobalt "poral" reaction. Note the punctate erythema, which has an almost petechial appearance.

FIGURE 2. A less regular, papular 48-hour cobalt reaction, again suggesting petechiae. The regular spacing suggests hair follicles, but, actually, acrosyringia are involved. Note the blue stain on the skin associated with cobalt patch-test materials.

lence of 18.3% non-allergic reactions to cobalt were observed by Fischer and Rystedt.[6]

This Study

In 1987, a group of residents I was training asked me about the unusual cobalt reactions we observed. Being aware of the studies described above, I told them confidently that these were "purpuric" reactions, even though that seemed amazing. I was so confident that I quickly doubted myself and we began to study these reactions.

Methods

Patch testing—When we first appreciated these unique false-positive cobalt reactions in 1988 and 1989, we realized that our own incidence data were imprecise and uncritical. Thus, the incidence data cited here are from a later testing period when we were more attentive to and critical of cobalt reactions.

Between May 3, 1993 and June 23, 1995, we tested 222 patients in the Contact Dermatitis Clinic at Oregon Health Sciences University for sensitivity to 1% cobalt chloride in petrolatum and to 2.5% nickel sulfate in petrolatum as part of our routine patch testing. Allergens were placed on Finn Chambers® and were adhered to the upper back with Scanpor® tape for 2 days. We then removed and read the results according to the criteria used by the NACDG[10] at 2 days and again at 5 or 7 days. The irritant ("poral") cobalt reactions were those that met the excellent descriptions of Cronin[3] and Fischer and Rystedt[6] cited above in the background comments (Figures 1 to 3). The results cited are the interpretations made at the final reading.

As part of the initial evaluations between June and November 1989 in our Contact Dermatitis Clinic, we also simultaneously patch-tested 51 patients to cobalt chloride 1% in petroleum, cobalt nitrate 1% in petrolatum, cobalt sulfate 1% in petrolatum, and ferric chloride 1% in petrolatum. Some of these reactions were biopsied.

Pathology—Patch-test reactions deemed cobalt irritant reactions, such as those seen in Figures 1 to 3, were biopsied at 48 hours and one was biopsied at 4 days. All of the reactions occurred on the upper back. Six-

Table I.

Incidence of Nickel and Cobalt Patch Test Reactions 1993–1995: 222 Patients

Irritant to cobalt	70 (32%)
also nickel allergic	12
Nickel-allergic (40 patients total [18%])	
also cobalt allergic	14
no cobalt reaction	14
Cobalt-allergic only	13
No reaction to nickel or cobalt	111
Total	222

teen patients provided 19 biopsies between November 1987 and January 1990. Patients ranged in age from 22 to 85 and consisted of nine men and seven women. Seventeen biopsies came from cobalt chloride reactions, and one each from a cobalt sulfate, and cobalt nitrate reaction in patients who also had cobalt chloride reactions.

Specimens were fixed in formalin and routinely stained. No special stains were used. The specimens were read by our pathologist, Dr. Clifton R. White, Jr. Many submissions contained the designation "petechial cobalt reaction." Dr. White was the first to recognize the unique changes in false-positive (irritant) cobalt patch-test reactions.

Results

Incidence of Irritant Cobalt Reactions—Forty (18%) of our patients from 1993 to 1995 were nickel allergic. Only 12 of these patients had irritant cobalt reactions, whereas 14 of them were deemed cobalt allergic and nickel allergic. The incidence of 32% irritant cobalt reactions remains fairly constant at the present time in our clinic (Table I).

Without repeat testing of the sort done by Fischer and Rystedt,[6] one could question that all 13 of our cobalt-allergic reactions were valid, inasmuch as isolated cobalt allergy is rare. In short, all patch testers realize that precise clinical separation of irritant from allergic reactions in patch testing is very difficult, even in unique situations such as the one described in this paper.

Reactions to Other Cobalt Salts—Of the 51 patients we tested simultaneously to other cobalt salts in 1989, 18 had "poral" cobalt reactions to at least one salt. None of them reacted to ferric chloride and four of them were allergic to nickel. Six showed irritant reactions only to cobalt chloride, 6 showed cobalt chloride reactions and also reacted to one other salt (5 to cobalt nitrate and 1 to cobalt sulfate), 2 reacted to all the cobalt salts with irritant "poral" reactions, and 4 failed to react to cobalt chloride but reacted to at least one other salt (3 to cobalt nitrate and 1 to cobalt sulfate) with poral reactions.

Histopathology

Five histopathologic patterns of change were noted. None of the 19 biopsies from the 16 patients demonstrated evidence of vasculitis, extravasated erythrocytes, or folliculitis.

Absence of Acrosyringial Change

Group 1: Epidermal Mononuclear Cells and Perivascular Mononuclear Cells—Two patients' biopsies showed sparse and superficial perivascular lymphohistiocytic infiltrates with many mononuclear cells throughout the epidermis.

FIGURE 3. Occasionally, the cobalt false-positive "poral" reaction spreads and appears to be a confluent purpuric-appearing plaque. This patch was biopsied and showed histology pattern 3 of epidermal necrosis with acrosyringial inflammation.

Group 2: "Unusual" Epidermal Spongiosis with Eosinophilic Keratinocytes—Two patients showed an "unusual" epidermal spongiosis with ballooning of epidermal cells. The keratinocytes had abundant eosinophilic cytoplasm. There was papillary edema. No acrosyringial units were seen, but the specimens' changes were believed to be similar to other "cobalt dermatitis" specimens that had been submitted to Dr. White.

Group 3: Epidermal Necrosis—Two specimens had prominent epidermal necrosis with a superficial mixed infiltrate containing lymphocytes and neutrophils. There were foci of spongiosis. The biopsies were considered as distinct from other cobalt biopsies examined. The acrosyringium showed localized inflammation. One of these biopsies was taken from the reaction seen in Figure 3.

Presence of Acrosyringial Change

Group 4: Localized Acrosyringial Inflammation—Two specimens (one obtained at 4 days) showed no epidermal spongiosis, but rather a superficial perivascular lymphohistiocytic infiltrate localized to the acrosyringium.

Group 5: Acrosyringial Disruption with Keratinocytic Vacuolization—Eleven specimens showed marked alteration of the acrosyringia with disruption of the spinous layer. There was pallor, an eosinophilic granular staining cytoplasm, and vacuolization of the keratinocytes at the acrosyringial opening. In some instances, the edema was mostly at the acrosyringium (Figures 4 and 5). There was occasional parakeratosis as well as a superficial perivascular lymphohistiocytic infiltrate.

Group 5 included one woman who was biopsied three times; (two cobalt chloride biopsies were taken 2 months apart; a third biopsy was of a "poral" cobalt nitrate reaction). Essentially, all specimens were microscopically identical. A man who had both a cobalt chloride and a cobalt sulfate reaction had both reactions biopsied at the same time. These reactions were essentially identical histologically and fell into the Group 5 type of histological change.

In our view, the 11 specimens in Group 5 are most definitive for the distinctive cobalt acrosyringial "po-

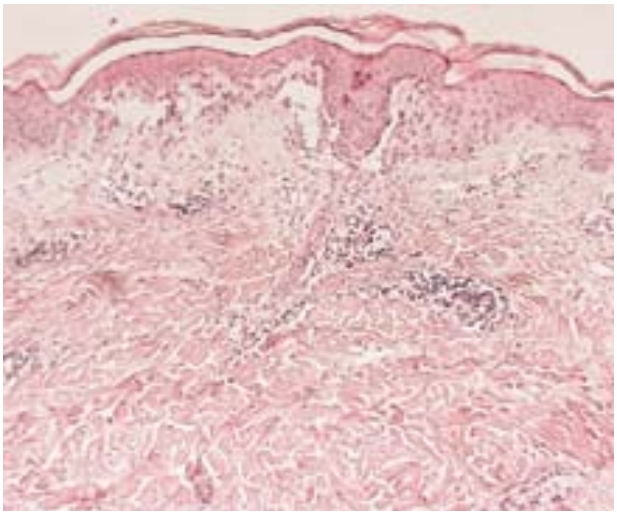

FIGURE 4. Cobalt reaction pattern 5 (acrosyringial disruption with kertinocytic vacuolization); the characteristic alteration of the acrosyringium with disruption of the spinous layer is obvious. In the dermis, there is a perivascular lymphohistiocytic infiltrate. Note the dermal extension of the eccrine sweat gland.

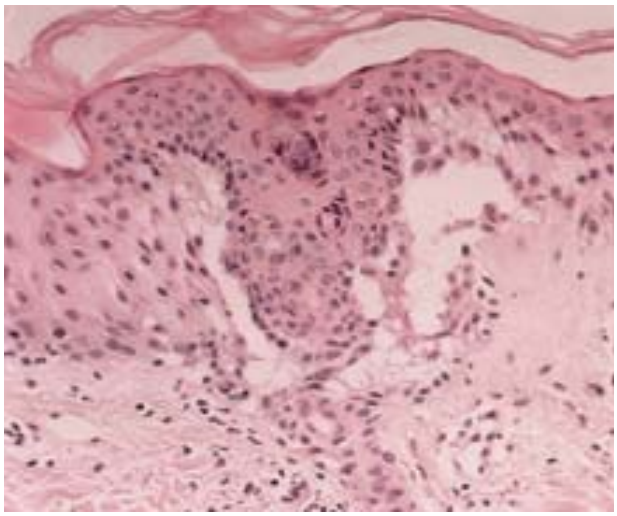

FIGURE 5. Close-up of the acrosyringium seen in Figure 4. Note the intracellular edema associated with intraepidermal and possibly subepidermal cells with displaced nuclei. There is no spongiosis or parakeratosis.

ral" reactions. Group 4 displays minimal acrosyringial change. Groups 1 through 3 probably represent changes near acrosyringia or changes too early to show more characteristic alterations (our biopsies were secured almost exclusively at 48 hours). Group 3 is a particularly interesting group in that cobalt is a known toxin (referred to by Schmidt *et al.*[4]). One must wonder whether this acrosyringial reaction we describe is not, in fact, the result of a toxic effect of cobalt on the acrosyringium. Certainly our third histological pattern of necrosis suggests such epidermal toxicity.

Discussion

The interpretation of patch-test reactions is not always simple. In my view, idiosyncratic reactions, such as those described in this paper, together with other subtleties involved in reading patch tests (let alone accurately diagnosing skin diseases likely to benefit from patch testing) should dictate that patch testing be performed mostly by dermatologists.[11] Certainly, many will disagree with me.

This study demonstrates that biopsying patch tests can occasionally be valuable. Understanding the histopathology of our clinical observations clarifies our interpretations. No reports of patch testing results mention the incidence of irritant or confusing reactions as mentioned above. The NACDG, for example, recently reported their results with no mention of irritancy.[12] Cobalt was given an 8% allergic incidence in the 1994 to 1996 report, and only 4.1% of the reactions were considered definitely relevant. We don't know how many of those patients were also nickel allergic. In personal discussions with the group, many members indicated that they don't even register the cobalt reaction as an irritant, since they now consider it to be unique to cobalt (as do we). In future studies of cobalt, or of unusual adnexal reactions with metals, we should probably be more specific in noting which reactions we include and which we exclude. The excellent dilutional studies of Fischer and Rystedt[6] mentioned previously highlight this point.

There is certainly room for further study of these cobalt reactions. They seem to occur usually, but not always, with petrolatum vehicles.[4,6] We don't know whether they could be reproduced on non-back skin. We don't know how far down the eccrine sweat duct or unit the effect extends, and we don't know how far down cobalt can be found. Our one specimen evaluated by electron microscopy was not helpful. Tissue analysis for cobalt localization would be of great interest.

Perhaps the most seductive aspect of this observation is the suggestion that cobalt may have a physiologic effect on eccrine sweat gland function, as have other metals such as aluminum.

Observing these reactions over time, and extending these histopathological inquiries to other metal patch-test reactions that we all assume are "follicular," could be of value as well. Perhaps changes could be seen microscopically before they are seen clinically.

All but two of the patients we biopsied had allergic patch-test reactions to other allergens. We didn't note their atopic state, but other studies have suggested that atopic or irritated skin or even other pos-

itive reactions may influence the prevalence of non specific or irritant reactions.[4-6,8]

Fischer and Rystedt[6] do not include histopathology in their "follicular" reaction study. We believe that Schmidt and colleagues[4] were probably describing reactions like our Group 1, 2, and 3 reactions, where no acrosyringium was seen. They do not describe epidermal changes. They mention erythrocytes, but show none in the photomicrograph they display.

In summary, the "poral" false-positive patch-test reactions seen with cobalt chloride seem to reflect a unique and probably toxic effect of cobalt on the acrosyringium. These reactions are neither follicular nor petechial and we believe that they are not allergic. As I age in this fascinating subspecialty, I see this phenomenon as yet another example of "All the Things I Knew Were True About Contact Dermatitis That Aren't."[1]

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