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Educational Case: Granulomatous Dermatitis

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.[1]

Keywords
pathology competencies, organ system pathology, skin, exogenous antigens, tattoo-related disorder, granulomatous dermatitis, noncaseating granulomatous dermatitis

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Primary Learning Objective

Objective SK3.1: Manifestations of Exogenous Antigens. Describe the clinical features and pathologic basis for skin manifestations to exogenous antigens including infectious organisms, drugs, chemicals, and environmental agents.

Competency 2: Organ System Pathology; Topic: Skin (SK); Learning Goal 3: Immune-Related Disorders of the Skin.

Patient Presentation

A 35-year-old Caucasian male presents to the dermatology office for concerns about a papule in the middle of his tattoo on his right forearm. The patient states that he noticed it several months ago and that it is itchy. His past medical history is unremarkable. He takes no medications. He has no recent travel history.

Diagnostic Findings, Part 1

Physical examination shows a 4-mm erythematous papule seen within the red pigmented portion of a multicolored tattoo on the patient's right forearm. The tattoo covers the dorsal portion of the patient's forearm. The tattoo is a design outlined with black ink and filled with areas of blue, green, yellow, orange, and red ink. The remainder of the tattoo and surrounding skin are unremarkable. Skin examination reveals no other abnormalities.

Questions/Discussion Points, Part 1

What Is the Differential Diagnosis Based on the Clinical Presentation?

The differential diagnosis of a small, itchy papule on an otherwise healthy 35-year-old male on the distal extremity would include an arthropod bite reaction, eczematous dermatitis, folliculitis, or possibly infection. The history specifically states that the papule is seen only within the red pigmented portion of his tattoo, and so the differential diagnosis would need to include a tattoo-related cutaneous reaction. A malignancy is unlikely given the patient's age. The history states that he is not on any medications, which helps to exclude a drug-related eruption.

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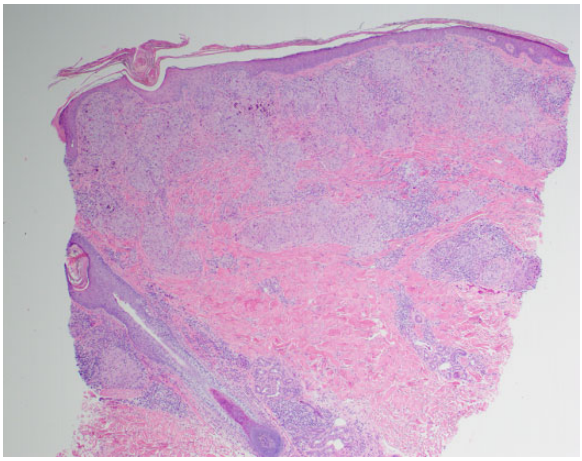

Figure 1. A punch biopsy of the patient's skin showing a noncaseating granulomatous dermatitis. There are well-formed clusters of histiocytes, some with surrounding lymphocytic inflammation, extending from the papillary dermis into the reticular dermis. The epidermis shows mild reactive change and orthokeratosis (hematoxylin and eosin, ×4).

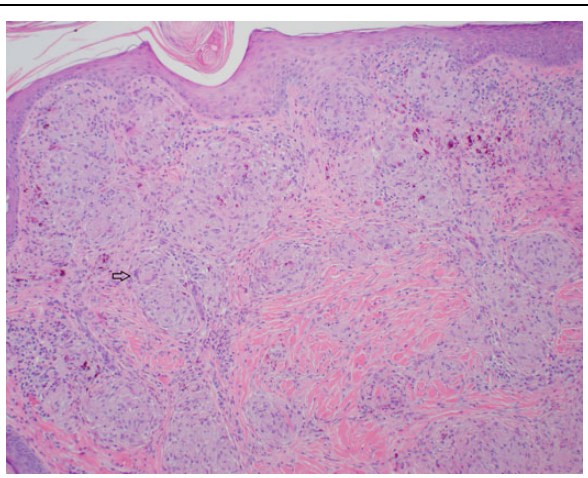

Figure 2. A medium-power view from the punch biopsy of skin highlighting the clusters of histiocytes with scattered giant cells (arrow). The histiocytes are identified by their abundant eosinophilic cytoplasm and ovoid nuclei. Red pigment is appreciated at this power, both within the granuloma and within the interstitium (hematoxylin and eosin, ×10).

Diagnostic Findings, Part 2

A Biopsy Is Performed of the Papule on the Patient's Forearm and Is Shown in Figures 1, 2, 3, and 4. What Does the Skin Biopsy Show on the Hematoxylin and Eosin–Stained Sections?

Figure 1 shows a punch biopsy of a dermal-based granulomatous infiltrate. There are tightly formed clusters of histiocytes, some with a surrounding rim of small lymphocytes, extending from the superficial papillary dermis into the mid-reticular dermis. The hair follicle shows mild perifollicular lymphocytic inflammation, as do the small vessels in the dermis. The epidermis shows focal reactive change and overlying orthokeratosis. Figure 2 highlights the clusters of histiocytes, identifiable by their abundant eosinophilic and vacuolated cytoplasm. Rare giant cells are also seen. Red pigment is seen scattered throughout the dermis. Figure 3 shows a high power view of a granuloma. Cytologically, the histiocytes contain ovoid to reniform nuclei with variably prominent nuclei and abundant eosinophilic cytoplasm. A thin rim of lymphocytes is seen on one edge. Red pigment is again seen, both within the histiocytes and in the interstitium. Figure 4 shows a higher magnification image of a granuloma, highlighting the red exogenous pigment located primarily within histiocytes.

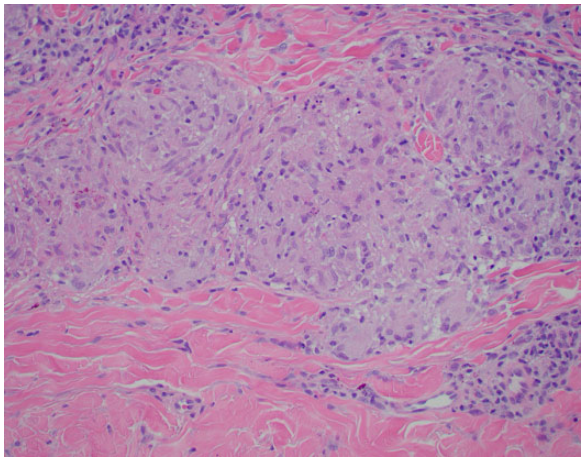

Figure 3. A high-power image of a granuloma from the punch biopsy of skin. The histiocytes are arranged in a tight cluster, with focal rimming of lymphocytes. Cytologically, the histiocytes contain ovoid to reniform nuclei and abundant eosinophilic and vacuolated cytoplasm. Exogenous red pigment is seen within the granuloma (hematoxylin and eosin, ×20).

What Additional Workup Can Be Performed to Narrow the Differential Diagnosis? What Additional History Could Be Helpful in Excluding Diagnoses?

Histochemical stains are performed to detect acid–fast bacilli (AFB stain), fungi (PAS stain), and bacteria (gram stain) and are negative, excluding an infectious etiology. Culture studies are performed and are negative for mycobacterial, fungal, and bacterial organisms. Polarization microscopy is negative for refractile material, ruling out a foreign body. Serologic studies for angiotensin-converting enzyme and chest X-ray are performed to exclude sarcoidosis.[2] Angiotensin-converting enzyme levels are normal. Chest X-ray shows no bilateral hilar lymphadenopathy.

Review of patient medications confirms that the patient is taking no medications to suspect a medication-induced process. There is no history of Crohn disease or rheumatoid arthritis to consider a cutaneous presentation of these diseases. There is no

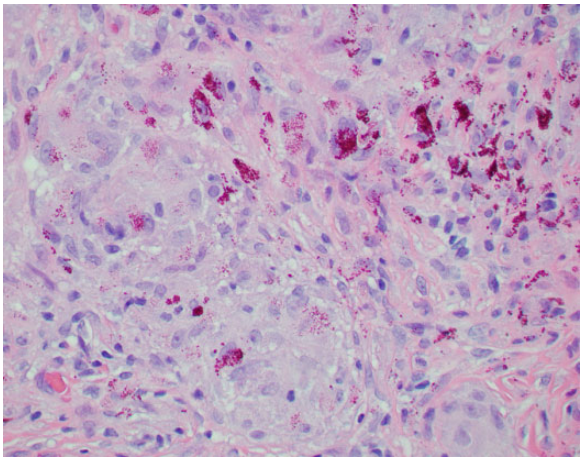

Figure 4. A high-power view of histiocytes containing exogenous red pigment. The pigment is coarse, and at this power, individual granules are visible. The histiocytes are notable for their variably prominent nucleoli, reniform nuclei, and abundant cytoplasm. Scattered lymphocytes can also be seen (hematoxylin and eosin, ×40).

documentation of prior malignancies or history of connective tissue disease, helping to exclude an interstitial granulomatous dermatitis or lichenoid and granulomatous dermatitis.

Questions/Discussion Points, Part 2

What Is Your Diagnosis Based on the Clinical Information and Microscopic Findings?

Clinical history of a healthy 35-year-old male with a single itchy, pink papule inside red tattoo area showing noncaseating, non-necrotizing granulomatous inflammation containing exogenous red pigment is consistent with a granulomatous tattoo reaction, a type of foreign body reaction. While there have been reports of cutaneous sarcoidosis presenting in areas of tattoo, the negative chest X-ray and negative serologic studies help to exclude sarcoidosis.[2,3]

What Is a Granulomatous Dermatitis?

A granulomatous dermatitis is a histologic pattern of inflammation in the skin. The inflammation is composed of non-neoplastic histiocytes and multinucleated giant cells and can be seen in a variety of arrangements.[4] Granulomatous dermatitides are many in number and variable in etiology and broadly can be divided into a non-necrotizing or non-necrobiotic group and a necrotizing or necrobiotic group.[5] Within those 2 categories, particular patterns can be seen.

In the non-necrobiotic and non-necrotizing category, one histologic pattern that is seen is termed "naked" granuloma, with the classic example being sarcoidosis. These granulomata are arranged as tight clusters of epithelioid histiocytes, specifically without surrounding inflammation—thus "naked." Similarly arranged clusters of histiocytes though with surrounding inflammation can be seen in reactions to foreign material (foreign body reaction) or infection (usually fungus). Non-necrotizing or non-necrobiotic granulomatous inflammation can also be seen as loosely arranged histiocytes within the dermis. The interstitial granulomatous dermatitides are examples of this form. The pattern in this patient's biopsy is best categorized as non-necrobiotic, non-necrotizing granulomatous dermatitis and would fit best in the epithelioid granuloma with surrounding inflammation pattern.

In the necrotizing or necrobiotic group, a palisading arrangement of histiocytes surrounding areas of various materials is seen. Granuloma annulare, rheumatoid nodules, or necrobiosis lipoidica (diabeticorum) show this palisading arrangement. Necrotizing granulomatous inflammation is most often seen in infectious cases, such as a mycobacterial infection.

Table 1. Histologic Classification of Cutaneous Granulomatous Dermatitides.

Necrobiotic or Necrotizing	Non-Necrobiotic or Non-Necrotizing
• Granuloma annulare • Necrobiosis lipoidica • Rheumatoid nodule • Lupus miliaris disseminatus faciei • Infectious	• Sarcoidosis • Foreign body reaction • Granulomatous rosacea • Elastolytic granuloma • Cutaneous Crohn disease • Granulomatous pigmented purpura • Interstitial granulomatous dermatitis • Lichenoid and granulomatous dermatitis • Infectious

What Is the Differential Diagnosis for a Non-Necrotizing, Noncaseating Granulomatous Dermatitis?

The differential diagnosis for a non-necrotizing, noncaseating granulomatous dermatitis is lengthy. The most commonly encountered entities include foreign body reaction, infectious causes, and sarcoidosis. The complete list can be found in Table 1.

What Causes a Granulomatous Reaction in Skin?

Most granulomatous infiltrates are caused by a type IV hypersensitivity reaction wherein a foreign antigen is processed by histiocytes and presented to T lymphocytes. The T cells then respond by secreting interleukins and other chemokines which recruit additional histiocytes to the site of reaction, producing a pathological granulomatous lesion. Reactions to the metal salts or other products contained in tattoo pigment can occur with many different pigments but is most commonly seen in red tattoos.[6,7] Red tattoo pigment can be either organic or inorganic.[8] The inorganic red pigments used in tattoos include mercury and mercury derivatives (cinnabar), cadmium selenide, and sienna (ferric hydrate). These toxic metals, found in red tattoo ink, are thought to cause a type IV hypersensitivity

reaction. Organic compounds such as vegetable dyes (sandalwood, brazilwood) have been used to replace mercury, but sensitivity can still occur. X-ray microanalysis has been used to determine the composition of red pigments and shown to contain a number of metallic elements including aluminum, iron, calcium, titanium, silicon, mercury, and cadmium.[9] Reactions may occur to one or more of the components, by similar type IV hypersensitivity reaction.

What Other Histologic Patterns Can Be Seen in a Tattoo-Related Skin Reaction?

Cutaneous reactions to exogenous red pigment include eczematous, lichenoid, pseudolymphomatous, granulomatous, and pseudoepitheliomatous. These patterns are important to recognize as they can be mistaken for other more ominous processes, such as carcinoma (pseudoepitheliomatous hyperplasia [PEH] pattern) or lymphoma (pseudolymphoma pattern).[8] Recognition of intralesional pigment is of utmost importance, particularly in situations without clinical history.[5,10]

Eczematous is another way of saying "spongiotic." A spongiotic dermatitis shows edema between keratinocytes in the epidermis. A lichenoid pattern is characterized by a band-like inflammatory infiltrate, often obscuring the dermal–epidermal junctional keratinocytes. A pseudolymphoma is a lymphoma-like lymphoid infiltrate of the dermis, often involving the superficial and deep dermis, surrounding vessels. What distinguishes pseudolymphoma (a reactive condition, a non-neoplastic process) from a lymphoma (a neoplastic process) is the presence of a mix of B cells and T cells rather than predominance of either B cells or T cells showing aberrant expression of antigen markers (meaning expressing proteins on their cell surface that they don't normally express). A granulomatous dermatitis, as seen in this case, is an infiltrate of non-neoplastic histiocytes. Pseudoepitheliomatous hyperplasia is characterized by irregular and extensive epidermal hyperplasia (irregularly thickened epidermis) with reactive cytologic changes (enlarged cells but with retained nuclear:cytoplasmic ratios). Pseudoepitheliomatous hyperplasia can closely mimic a well-differentiated squamous cell carcinoma. Tattoo-related reactions can present as any one of these histologic patterns.

Teaching Points

1. Tattoo ink is a common exogenous pigment found in skin biopsies and can cause a type IV hypersensitivity reaction.
2. Red tattoo pigment is most frequently implicated in tattoo-related reactions.
3. Histologically, tattoo-related reactions can take of the form of an eczematous dermatitis, lichenoid dermatitis, granulomatous dermatitis, pseudolymphoma, or rarely PEH.
4. A granulomatous dermatitis is a dermal histiocytic infiltrate which can be arranged in a variety of patterns.
5. Granulomatous dermatitides can be histologically classified broadly into either necrobiotic or necrotizing and non-necrobiotic or non-necrotizing patterns.
6. The histologic differential diagnosis for a granulomatous dermatitis is broad and therefore particular attention to architectural arrangement of the histiocytes is necessary to narrow the differential. Additional workup is often necessary to arrive at a particular etiology (eg, serologic studies, radiography, infectious studies, correlation with patient medication, and past medical history).

Declaration of Conflicting Interests

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