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Senior Resident Peer-to-Peer Case Studies

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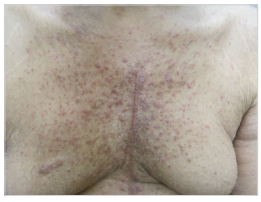
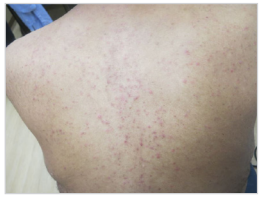
Case Studies authored by our educational partner GW School of Medicine and Health Sciences Dermatology Residency Program

School of Medicine & Health Sciences
THE GEORGE WASHINGTON UNIVERSITY

1)

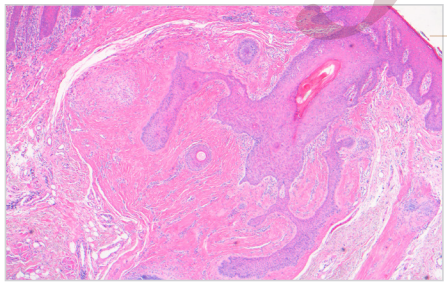




A 67-year-old African American male recently diagnosed with metastatic renal cell carcinoma presents to clinic for evaluation of pruritic and burning skin findings (see clinical images below) that developed two weeks after he started treatment with bevacizumab and erlotinib. Which of the following medications would not cause this eruption?

A. Cetuximab
B. Erlotinib
C. Panitumumab
D. Bevacizumab
E. Gefitinib

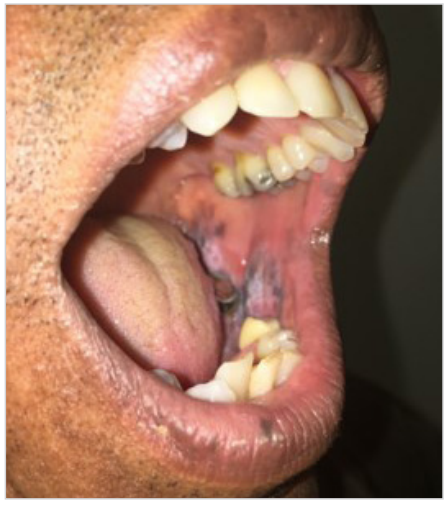
2)



34-year-old Caucasian female presents for evaluation of several skin-colored papules on the cheeks. She notes her mother and sister have similar findings. A biopsy is done and pathology results are shown below. Which of the following is true about this disorder?

A. It is inherited in an X-linked recessive fashion.
B. These patients should be referred to nephrology and pulmonology.
C. Spiradenomas and cylindromas may also be found in this patient.
D. It is due to a mutation in the *PTEN* gene.
E. Mohs micrographic surgery is indicated for treatment of these tumors.

3)



After starting multiple new medications in the past four months a 58 year-old man presented to clinic with a nonpainful discoloration on his left buccal mucosa for the past three weeks. He also had a recent sinus infection treated with oral antibiotics. He denied tobacco use, alcohol use, and any dental work in the past three years. Biopsy showed focal hypergranulosis, necrotic keratinocytes, a jagged mucosal undersurface, and a lymphocytic infiltrate in the upper submucosa with scattered eosinophils and a few melanophages.

A. Amoxicillin/clavulanate
B. Azithromycin
C. Lorazepam
D. Lisinopril
E. Metformin

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Senior Resident Peer-to-Peer Case Studies

The content of these case studies, ideal to review during peer study groups, was developed by Elizabeth Robinson, MD and Jennifer Aronica, MD under the guidance of dermatologist Adam Friedman, MD, FAAD, Associate Professor of Dermatology, Residency Program Director, Director of Translational Research, Department of Dermatology GW University.

Elizabeth Robinson, MD
GW School of Medicine
and Health Sciences,
Department of Dermatology

Jennifer Aronica, MD
GW School of Medicine
and Health Sciences,
Department of Dermatology

Answers

1) The correct answer is D: Bevacizumab would not cause this skin eruption.

Explanation/Literature Review

This patient has a papulopustular drug eruption associated with erlotinib, an epidermal growth factor receptor inhibitor (EGFR-I). Acneiform eruptions with EGFR-I use can be seen in more than 75% of patients treated with these agents and is more common with the monoclonal antibodies, cetuximab and panitumumab, than the low molecular weight tyrosine kinase receptor inhibitors like erlotinib and gefitinib. EGFR is involved in regulating keratinocyte proliferation and normal differentiation of the hair follicle. Inhibition of EGFR allows for the production of several inflammatory cytokines and recruitment of inflammatory cells in the dermis coupled with disruption of hair follicle growth which leads to the characteristic papulopustular eruption localized mostly to hair follicles.

The eruption, which mostly affects the trunk, face and scalp accompanied by pruritus, burning or pain, usually occurs within the first two weeks of treatment and resolves within a month once EGFR-I therapy is stopped. Discrete erythematous papules and pustules in areas with high numbers of sebaceous glands are seen on exam without comedones. Patients can experience mild, almost prodromal symptoms of burning or erythema before the appearance of papules and pustules. Some risk factors for development include higher medication doses and sun exposure.

Other cutaneous side effects of EGFR-I therapy includes both scarring and non-scarring alopecias, hair textural changes, paronychia, pyogenic granuloma-like lesions, pruritus, trichomegaly, seborrheic dermatitis, photosensitivity and stomatitis.

There are four grades used to classify the severity of these reactions. Grade 1 involves papules and pustules covering less than 10% BSA, while grade 2 involves papules and pustules over 10-30% BSA but also with symptoms of pain or pruritus that limits daily activities. Grade 3 affects more than 30% BSA with symptoms of pain and pruritus, difficulty with self-care and local superinfection warranting oral antibiotics. Grade 4 reactions include greater than 30% BSA affected with pain and pruritus plus extensive superinfection requiring IV antibiotics. Interestingly, for NSLC and metastatic colon cancer, severity of the papulopustular rash has been correlated with better antitumor responses.

Of note, development of this eruption is not a contraindication to continue EGFR-I chemotherapy nor does it preclude future use of a different EGFR-I. However, it is important to mitigate symptoms or even prevent development since this eruption can lead to temporary discontinuation of the medication and patient reported lower quality of life. One study looking at EFGR-I therapy dermatologic toxicities found that rash as opposed to xerosis, paronychia and pruritus, led to a greater decrease in quality of life scores and that emotional well being and daily functioning in activities was affected by the papulopustular eruption.

Since there is such a high incidence and frequent patient discomfort associated with this eruption, it often warrants treatment based on severity. For mild grade 1 reactions, topical acne medications like clindamycin, benzoyl peroxide, metronidazole and erythromycin can be used. In grade 2 reactions, the same topical medications should be used in addition to an oral tetracycline like doxycycline or minocycline and an antihistamine for pruritus. Additionally, topical steroids and/or retinoids in conjunction with an oral tetracycline has been effective. Reports have also showed that oral isotretinoin is efficacious however since EGFR-I therapy can also cause paronychia and xerosis, patients should be appropriately counseled. For grade 3 reactions, EGFR-I treatment may need to be delayed to allow for treatment with oral tetracyclines to reduce inflammation. In grade 4 reactions, treatment with EGFR-Is should be discontinued and patient may require management by a burn unit.

Answer choice D, bevacizumab, is a humanized monoclonal antibody against vascular endothelial growth factor (VEGF). Bevacizumab is FDA- approved used to treat metastatic colon cancer, lung cancer, renal cell carcinoma, certain brain cancers and age-related macular degeneration. Bevacizumab is not known for causing cutaneous reactions but several potential side effects include hemorrhage, gastrointestinal perforations, impaired wound healing, hypertension, blood clots, thrombocytopenia, diarrhea and xerosis.

2) The correct answer is B. These patients should be referred to nephrology and pulmonology.

Explanation/Literature Review

This is an image of a fibrofolliculoma which is seen in Birt-Hogg-Dubé syndrome (BHD). BHD is due to an autosomal dominantly inherited germline mutation in the FLCN gene which encodes the protein folliculin and can affect the skin, kidneys and lungs. It is an autosomal dominant genodermatosis.

The proposed guidelines for diagnosis of BHD require either one major or two minor criteria. The major criteria include at least five fibrofolliculomas or trichodiscomas with adult onset or a pathogenic FLCN germline mutation. Pathology of a fibrofolliculoma reveals strands of immature follicular epithelium radiating from a central follicular-like structure surrounded by a pink fibrous orb. Trichodiscomas are fibrofolliculomas cut in a plane section where the epithelial strands are not shown. Fibrofolliculomas usually occur on the face and upper trunk and patients may develop new ones throughout adulthood. They are the most common skin manifestation of BHD which can also have acrochordons, trichodiscomas, hyperseborrhea and multiple epidermoid cysts.

The minor criteria are a first degree relative with BHD, multiple lung cysts in the lower lobes with or without history of spontaneous pneumothorax, and early onset or bilateral renal cell cancer. Patients with BHD should start surveillance with pulmonology and nephrology beginning at 20 years old and also be referred for genetic counseling. Pulmonology may get baseline CT imaging at diagnosis to evaluate any existing lung disease. Smoking can increase the risk of developing a pneumothorax so this should be advised against. Patients with BHD have a risk seven times greater than the general population for developing a renal tumor and almost one third of patients will develop one. The most common histologic type of RCC in BHD is the chromophobe, followed by oncocytomas and mixed variants. Although there are no set guidelines for when to start and how frequently to monitor, renal imaging should be used for monitoring with either CT or MRI which are more accurate than ultrasound.

Answer choice C describes Brooke-Spiegler syndrome which is caused by a mutation in CYLD, a tumor suppressor gene, and is inherited in an autosomal dominant pattern. It is characterized by three adnexal tumors including cylindromas, spiradenomas and trichoepitheliomas which usually appear in late childhood or early adolescence and patients can continue to develop new ones throughout adulthood. These tumors are generally benign and do not require intervention however they can be disfiguring and depending on location or size they could cause problems with vision or hearing. There is also the potential for malignant transformation into cylindro- or spiroadenocarcinoma. Patients are also at higher risk of developing basal cell carcinomas, thus patients should have regularly skin checks with their dermatologist.

Answer choice D describes Cowden syndrome which is a hamartomatous disorder characterized by cutaneous findings of facial trichilemmomas, punctate palmoplantar keratoses, lipomas, skin tags, sclerotic fibromas, and oral papillomas. Cowden syndrome is due to an autosomal dominant mutation of PTEN, a tumor suppressor gene. Hamartomas can involve of other organ systems, the most common being thyroid, breast and gastrointestinal. Thyroid findings include adenomas, goiters and the most important to surveil for, follicular carcinoma. Patients are at a higher risk of developing fibrocystic change and fibroadenomas of the breast and also adenocarcinoma, the most common malignancy occurring in Cowden syndrome which occurs in almost half of women with Cowden syndrome. Patients can also have hamartomatous polyps in the colon but these have a low risk of malignant transformation. Lhermitte-Duclos disease, a gangliocytoma of the cerebellum, is one of the criteria for Cowden syndrome and leads to increased intracranial pressure and seizures. Management should focus on monitoring for malignancy and patients will need to have close follow-up with several different specialists.

Answer choice E would make sense if these were basal cell carcinomas (BCC), as seen in Basal cell nevus syndrome (BCNS) however the pathology represents a fibrofolliculoma. BCNS is due to an autosomal dominant mutation in the PTCH gene, a tumor suppressor protein in the sonic hedgehog signaling pathway. In addition to multiple BCCs, patients have abnormalities of bones, central nervous system, soft tissues, eyes and endocrine system. Diagnosis is based on either major criterion and molecular confirmation, two major criteria or one major and two minor criteria. The hallmark major criterion is the diagnosis of multiple BCCs, that can be early in onset around puberty and may resemble melanocytic nevi, acrochordons or seborrheic keratoses. Major criteria also include palmoplantar pits, asymptomatic odontogenic keratocysts of the jaw, calcification of the falx cerebri and may develop medulloblastoma during infancy. Minor criteria are cleft lip or palate, ovarian/cardiac fibroma, ocular abnormalities, macrocephaly, rib anomalies, skeletal abnormalities. Treatment involves frequent skin checks, biopsy of suspicious lesions and treating BCCs with standard methods with or without the addition of vismodegib or sonidegib, both smoothened inhibitors. These medication decreases BCC tumor burden and prevents new BCCs, however due to side effects like dysgeusia, hair loss and muscle aches, half of patients discontinue due to poor tolerability.

3) The correct answer is D. Lisinopril is the most likely cause of the discoloration on his left buccal mucosa.

Explanation/Literature Review

Causes of white and pigmented discoloration on the buccal mucosa include leukoedema, leukoplakia, oral lichen planus, candidiasis, and contact reactions, including amalgam. This patient's biopsy is consistent with a lichenoid reaction. Multiple eosinophils are indicative of a possible drug-induced lichen planus. Causes of lichenoid drug eruptions include: gold, antimalarials, quinidine, penicillamine, amphetamines, thiazides, ACE inhibitors, TNF-alpha inhibitors, and statins. Drug-induced oral lichen planus is most commonly caused by NSAIDs, sulfonylureas, antimalarials, HIV antiretrovirals, beta-blockers, and ACE inhibitors. Though the oral mucosa is often spared in lichenoid drug reactions compared to lichen planus, oral lichenoid drug reactions may occur with or without skin involvement. Unlike oral lichen planus, drug-induced oral lichen planus is usually unilateral. Drug-induced lichen planus may take many months to develop and weeks-to-months to resolve after stopping the medication, often with long-lasting dyspigmentation.

References Question 1

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References Question 2

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References Question 3

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