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Dermatologic side effects associated with the MEK 1/2 inhibitor selumetinib (AZD6244, ARRY-142886)

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Abstract:

Background: Selumetinib (AZD6244, ARRY-142886) is a second generation MEK inhibitor that is currently in clinical trials for various solid malignancies. MEK kinase inhibitors are associated with dermatologic toxicities. While reactions affecting the skin, hair and nails to other targeted agents, such as epidermal growth factor receptor inhibitors (EGFRIs) have been abundantly described in recent years, the dermatologic toxicities associated with MEK inhibitors have not been well characterized. Similarly, their management may present a challenge in clinical trials. We reviewed the clinical presentation, evolution and management of dermatologic toxicities associated with selumetinib.

Methods: A retrospective review of medical records of 11 patients referred to the Dermatology Service with dermatologic toxicities secondary to selumetinib was performed. Data from two phase II trials in which selumetinib was used to treat advanced metastatic cutaneous, mucosal, or uveal melanomas were reviewed. Parameters studied included the time to onset, clinical presentation, histology and management. In addition, the clinical database was accessed to retrieve clinical photographs when available.

Results: Eight patients received selumetinib suspension orally at 100 mg twice a day and three patients received a newer capsule formulation at the maximum tolerated dose of 75mg with the same frequency. The following adverse effects were observed: papulopustular rash (100%), xerosis (36%), pruritus (45%), fissures (9%), telangiectasias (27%), hyperpigmentation (9%), alopecia (9%), angular cheilitis (9%), and paronychia (9%). In addition, secondary bacterial infection with *Staphylococcus aureus* was documented in 3 patients (27%).

Conclusions: Dermatologic side-effects associated with selumetinib were similar to those seen with epidermal growth factor receptor inhibitors (EGFRIs). Treatment approaches used for EGFRi-induced dermatologic reactions may be potentially utilized to manage those associated with selumetinib.

Keywords: selumetinib, papulopustular rash, dermatologic toxicity, MEK inhibitor

Introduction:

The Raf/MEK/Erk mitogen-activated protein kinase (MAPK) cascade is a molecular pathway that transduces signals from the cell surface to the nucleus, regulating normal cellular survival, proliferation, and differentiation. Activating mutations of this pathway, at the level of a tyrosine kinase receptor (e.g. EGFR), RAS, or BRAF, can lead to constitutive activation, driving malignant behavior. In malignancies driven by activating mutations of EGFR, inhibitors of the receptor can lead to significant anti-tumor effects. These EGFRIs are commonly associated with well-characterized dermatologic toxicities, which include papulopustular (acneiform) rash, xerosis, pruritus, paronychia, hair modifications including alopecia, hyperpigmentation, and telangiectasias [1]. Inhibitors of RAF lead to a clinically distinct constellation of dermatologic side effects [2, 3]. Since the known upstream activating mutations converge on MEK, a recent strategy has been to develop inhibitors of a MEK kinase, such as selumetinib. This agent has shown excellent preclinical activity in a variety of tumors including colorectal, pancreatic, non-small lung, hepatocellular cancers, and melanoma [4-7]. The MEK inhibitors CI1040, PD-0325901, and selumetinib tested to date in clinical trials have been associated with a skin rash [8-10]. The dermatologic reactions caused by these agents have not been previously described in detail in the literature. However, their description is of importance in the understanding of side effects to widely used EGFR and RAF inhibitors. One recent case series presented a spectrum of dermatologic side-effects of selumetinib that resembled those seen with EGFRIs [11]. This retrospective review will describe the clinical presentation and evolution of several dermatologic reactions associated with selumetinib and will discuss available and potential therapeutic interventions.

Methods: A retrospective review of medical records of 11 patients referred to the Dermatology service with manifestations of dermatologic reactions secondary to selumetinib was performed. The data from two phase II trials in which selumetinib was used to treat advanced metastatic cutaneous, mucosal, or uveal melanomas was reviewed. Eight patients received selumetinib suspension orally at 100 mg twice a day and three patients received a newer capsule formulation at the maximum tolerated dose of 75mg with the same frequency. Both of these trials were approved by the institutional review board (IRB) and all patients signed a consent form. Parameters studied included the time to onset, clinical presentation, evolution, routine histopathology (hematoxylin and eosin-stained sections for formalin-fixed and paraffin embedded skin biopsies) and complications of various dermatologic reactions. In addition, the clinical database was accessed to retrieve clinical photographs of these dermatologic findings when available.

Results:

Case 1

A 58 year-old male had a history of mucosal melanoma, first diagnosed 10 years earlier and treated with multiple surgeries and radiotherapy. Three months after presenting with metastatic disease to the lung, mediastinum, and the left adrenal gland, he started treatment with selumetinib. The patient noticed the onset of the rash on the 5th to 6th day of therapy, initially manifesting as non-pruritic follicular papules on the upper chest. It progressed on the 12th day to an acneiform eruption affecting the face, post-auricular areas, neck, and upper torso. Over the course of the first month the lesions evolved from papules into a papulopustular rash with many crusted lesions, for which the patient had been treated with moisturizer creams and oral

diphenhydramine for symptomatic relief of pruritus. Selumetinib was continued at the same dose. When seen in Dermatology service one month after starting therapy, the rash extended from the face to buttocks and upper arms, covering more than 50% of body surface area (BSA), accompanied by erythema. The lesions were especially dense and coalescing around the central aspect of the face (**Figure 1**). Pruritus was limited to post-auricular and paranasal areas. A culture of one of the nasal pustules was obtained and the patient was treated with a one week course of oral cephalexin 250 mg four times daily, topical mupirocin and triamcinolone 0.1% creams. Ten days later, there was resolution of pustules and crusts, with persistent but significantly improved papular lesions in a similar distribution, sparing the buttocks. The culture was positive for *Staphylococcus aureus*. Topical therapy was continued but a stable rash persisted for the next month. Selumetinib was discontinued after approximately 2 months of treatment after disease progression and development of pulmonary emboli that were likely related to his underlying disease. The rash gradually resolved over the course of one month, with residual scars in areas previously affected by the papulopustular rash.

Case 2

A 53 year-old female had a 1.5mm thick malignant melanoma on the right upper arm treated with a wide excision. After twelve years she presented with regional recurrence and metastatic disease to the lungs, and selumetinib was initiated two months later. Due to asymptomatic bradycardia identified by an EKG one week after treatment, selumetinib was temporarily discontinued. However, bradycardia was felt to be unrelated to the drug, and it was subsequently restarted at the same dose one week later. The patient noticed the onset of a facial rash within 2 weeks of restarting the drug. The rash progressed during the first month and by the

27th day, when seen by the Dermatology service, multiple papules affecting the scalp, face, neck, and the chest were seen. The patient also developed hyperkeratosis and fissures of the heels. She was treated with topical clindamycin phosphate 1% solution for the scalp, clindamycin/benzoyl peroxide gel and pimecrolimus 1% cream for the face, clindamycin/benzoyl peroxide gel for the chest, and emollients for fissures. Minimal fissures of the heels and distal finger tufts with significant reduction in the overall erythema and number of lesions were evident 6 weeks later (**Figure 2**). Selumetinib was discontinued shortly prior to this appointment due to lack of response, but the patient reported improvement even prior to cessation of therapy. There was near complete resolution of the rash with minimal residual papules on the mid chest 6 weeks after interruption of treatment.

Case 3

A 51 year-old female with a history of multiple primary cutaneous melanomas developed metastatic disease 10 years after her initial diagnosis and started treatment with selumetinib. The patient noticed the onset of a non-pruritic acneiform rash involving the face and neck on the 5th day of treatment. She was referred to Dermatology, and physical examination on the 8th day demonstrated erythematous papules, particularly affecting the chin and cheeks (**Figure 3**). She was treated with a 10-day course of oral cephalexin 500 mg four times a day and topical metronidazole cream. Multiple erythematous papules and pustules on the central forehead and cheeks with occasional lesions on the back were seen on the 15th day. The patient was non-compliant with treatment and she was encouraged to complete the course of antibiotics and continue topical therapy. Four weeks later, significant improvement of the rash with only few facial papules and pustules were evident. Over the course of the next 6 weeks, the rash resolved

with persistent mild facial erythema. Gradual improvement in erythema was followed by persistent xerosis over the next 8 weeks, at the end of which, the drug was discontinued due to disease progression. Xerosis gradually resolved over the next month.

Case 4

A 52 year-old female with uveal melanoma presented with metastatic disease 5 years after the initial diagnosis. Initial treatment with temozolomide was changed to selumetinib two months later due to disease progression. She noticed the onset of a facial rash approximately 1 week after starting therapy, which progressed over the course of the first month. Physical examination by the Dermatology service 4 weeks after starting therapy revealed multiple erythematous acneiform papules in the central aspect of the face, neck, and upper torso, with few scattered lesions on the upper arms. She had been using oral diphenhydramine for pruritus and topical triamcinolone 0.1% cream with some improvement. The patient also reported increased alopecia. Topical mupirocin cream was added and the patient was encouraged to use an antibacterial cleanser and emollients. The facial rash resolved by the end of the following month. However, a maculopapular rash extending from the neck to the lower trunk, covering approximately 60% of BSA persisted throughout the 3 months of treatment. After 3 months of therapy, she developed pain in her right index finger and physical examination demonstrated periungual erythema, particularly affecting the right index finger and some of her toes. This paronychia was treated with a 4% thymol preparation. By the end of the 4th month, the rash progressed and multiple folliculocentric erythematous papules with a few pustules extending from the face to the buttocks were seen. Similarly, there was paronychia of the right 2nd and 1st fingers and a portion of the right 2nd nail appeared to be ingrown. The patient also developed

bilateral angular cheilitis. One of her pustules was cultured and she was treated with oral cephalexin, topical triamcinolone 1% and mupirocin creams. Paronychia was treated with silver nitrate and topical mupirocin after the ingrown portion of the nail was resected and cultured. Angular cheilitis was managed with topical econazole nitrate and topical hydrocortisone 2.5% creams. Both cultures were positive for *Staphylococcus aureus*. Interruption of therapy due to dermatologic toxicities resulted in significant improvement of the rash and resolution of paronychia over the course of the next two weeks. Selumetinib was restarted at 50% of the original dose. There was recurrence of paronychia and progression of the rash one week after restarting therapy, and erythematous papules were seen extending from the face to the chest along with mild erythema, edema, and tenderness of the right thumb. The 1st right nail was dystrophic (**Figure 4**). Scattered facial telangiectasias were evident. Topical therapy was continued for the rash and paronychia was treated with topical econazole and hydrocortisone 2.5% creams. The rash gradually improved over the next 3 months, when selumetinib was discontinued due to progression of disease. Complete resolution of the rash was evident 4 months after treatment cessation.

Case 5

A 76 year-old male with metastatic choroidal melanoma and psoriasis was initially treated with temozolomide, which was changed to selumetinib due to progression of disease. Xerosis was noted during the 4th week of treatment. Approximately after 7 weeks of therapy, the patient noted a mildly pruritic erythematous rash. When seen by the Dermatology service 2 weeks later, he had folliculocentric, erythematous crusted papules and pustules, more pronounced on lower than upper extremities, with few lesions on the trunk. There was also left

lower leg cellulitis. Secondary folliculitis was suspected, and after culturing a pustule the patient was treated with a 10-day course of oral cephalexin 250mg four times a day and topical mupirocin, with significant improvement over the course of the next three weeks. The culture was positive for *Staphylococcus aureus*. Approximately after 4 months of selumetinib treatment, scattered eczematous xerotic patches were seen, for which the patient had been using topical corticosteroids with partial improvement. During the 5th month of therapy, there was recurrence of a mildly pruritic rash involving the arms and legs, which was treated with topical clobetasol and a 10-day course of oral cephalexin 500mg. There was gradual resolution over the course of the next three weeks, with fading erythema and hyperpigmented macules in the previously affected sites. Xerosis with scaling and scattered eczematous lesions remained throughout the treatment.

Clinical presentation, treatment and duration of cutaneous findings for the remaining six patients can be found in Table 1.

Discussion:

Several different MEK kinase inhibitors have been tested in clinical trials. A skin rash was reported as one of the more common side effects of the agents investigated thus far [8-10, 12]. The first selective agent to be clinically tested was CI-1040. A mild and reversible acneiform rash, predominately affecting the face and upper torso, was seen in 14 out 77 patients in its phase I study [8]. Selumetinib is an orally available, second generation MEK inhibitor. Erythematous maculopapular rash predominately affecting the torso was the most frequent (74%), dose dependent, and dose limiting toxicity of this drug in its phase I trial [10]. The majority of the cases were mild to moderate in severity and resolution typically followed drug

interruption and/or dose reduction. In our analysis of 11 patients we observed erythematous papulopustular rash, acute paronychia, xerosis cutis, pruritus, fissures, telangiectasias, hyperpigmentation, increased alopecia, and angular cheilitis (Table 2). This spectrum of dermatologic adverse effects resembles toxicities of EGFRIs.

A papulopustular rash is the most common side effect of EGFRIs, seen in up to 90% of patients and is most commonly mild to moderate in severity [13]. The rash in our patients with regard to its severity, onset, accompanying pruritus and erythema, evolution from papules to papulopustular lesions with crust formation in some cases, and involvement of seborrheic rich areas and the trunk was very similar to the rash of EGFRIs [13-15]. Similarly, discontinuation of selumetinib resulted in improvement and resolution of symptoms. Three patients developed secondary superinfection with *Staphylococcus aureus*. The two major histopathological patterns of EGFRi-induced papulopustular rash include perifollicular superficial dermal inflammatory infiltrate and superficial neutrophilic suppurative folliculitis [16]. A biopsy of the right upper back rash in patient #11, approximately 4 weeks after its onset, revealed mild spongiotic dermatitis and perifollicular dermal mixed cell infiltrate composed of lymphocytes, neutrophils, plasma cells and histiocytes associated with edema, similar to the changes seen with EGFRIs (Figure 5 and 6).

Paronychia is a less common toxicity of EGFRIs. This periungual inflammation is characterized by pain, erythema, and swelling of nailfolds that can potentially progress to a pyogenic granuloma-like lesion, mimicking an ingrown nail [17]. Selumetinib-induced paronychia, characterized by delayed onset, erythema, swelling, an ingrown nail, and resolution upon treatment interruption, closely resembles paronychia due to EGFRIs [18]. The etiology of

EGFRIs periungual inflammation does not appear to be infectious in origin, but secondary superinfection with *Staphylococcus aureus* can occur [2]. Similarly, a superinfection with *Staphylococcus aureus* was documented in case 4.

Xerosis can be observed in up to 35% of patients treated with EGFRIs [17]. Involvement of feet or hands can result in fissures, which can be quite painful [19]. Four of our patients gradually developed xerosis, in one case manifesting with scaling and patchy eczematous lesions. Fissures involving bilateral heels and distal finger tufts were seen in one patient. Alopecia, a late adverse effect, can be seen in approximately 5% of patients treated with EGFRIs, manifesting after several months of treatment [1]. One patient in our series reported worsening of her pre-existing alopecia. Hyperpigmentation can develop in regions previously affected by EGFRi-induced rash, usually manifesting after 1-2 months of treatment [17]. Similarly, residual hyperpigmentation was seen in case 5, following resolution of the rash involving the extremities. Telangiectasias can develop in areas affected by the papulopustular rash secondary to EGFRIs [17]. Three patients treated with selumetinib developed scattered telangiectasias in the regions affected by the skin eruption.

In our series, dermatologic side effects of selumetinib are similar to those of EGFRIs with respect to the spectrum, clinical presentation, evolution, and potential complications such as a superinfection. Epidermal growth factor receptors (EGFRs) have been shown to play a critical role in normal keratinocyte proliferation, differentiation, and survival [20]. Inhibition of these receptors and downstream signaling cascades leads to keratinocyte cell death, decreased cell migration, and inflammation, which contribute to dermatologic toxicities of EGFRIs [1]. Our data suggests that inhibition of the MAPK pathway in keratinocytes, either at the level of EGFR

or at the level of MEK causes similar dermatologic toxicities. This suggests that the treatment approaches used in EGFRi-induced reactions [15, 18] may also be useful for treating dermatologic side effects caused by MEK inhibitors.

Topical triamcinolone, metronidazole, clindamycin, or mupirocin with or without an oral antibiotic were used to treat the skin rash in our patients, similar to proposed guidelines for the treatment of EGFRi rash [15]. Even in the absence of an active infection these guidelines suggest the use of semisynthetic antibiotics such as doxycycline or minocycline for moderate to severe cases. If the rash is secondarily infected, several antibiotics may be effective if chosen appropriately, but doxycycline or minocycline may provide additional benefit secondary to their weak anti-inflammatory properties [13]. It is important to remain vigilant for secondary superinfections in patients treated with MEK inhibitors. A recent review demonstrated that patients with dermatologic toxicities from EGFRi demonstrate a high prevalence of infectious complications, particularly with *Staphylococcus aureus*. Most of these infections are seen in seborrheic-rich areas and at sites affected by dermatologic adverse effects [21]. Although it remains to be demonstrated, patients treated with selumetinib may have a compromised barrier function of the epidermis with structural changes similar to those of EGFRi, increasing their risk of infections, particularly with *Staphylococcus aureus*. Lastly, topical pimecrolimus was used in one of our patients. However, a recent prospective randomized trial of topical pimecrolimus for a cetuximab-induced eruption did not result in a clinically significant benefit [22], and may not represent an effective treatment option for selumetinib induced rash. Future trials would be needed for clarification.

Severe paronychia in our patient was treated with resection of a part of the nail, topical silver nitrate, mupirocin, oral antibiotics, and subsequently a combination of topical antifungal and corticosteroids creams. Topical corticosteroids and oral antibiotics such as minocycline and doxycycline have been successfully used in EGFRi related paronychia, with silver nitrate and antiseptic soaks used in more severe cases with granulation tissue. Partial nail-plate excision has been utilized as well [17]. Perhaps, preventative strategies such as avoiding tight fitting shoes, nail biting, excessive friction and pressure on periungual tissues, a crucial component of managing patients on EGFRis, can be used in patients treated with MEK inhibitors.

Xerosis and fissures can be managed with emollients (Eucerin or Cetaphil creams) and patients should be instructed to use tepid water, minimize showering, and avoid alcohol-based skin care products.

MEK 1/2 inhibitor selumetinib is currently being evaluated in clinical trials. It is associated with high prevalence of a rash, as was seen in its Phase I trial. In addition, our retrospective review with other reported case series [11] demonstrate other associated dermatologic disorders such as a papulopustular rash, paronychia, xerosis cutis, pruritus, fissures, telangiectasias, hyperpigmentation, increased alopecia, and angular cheilitis. Due to their similarities to dermatologic reactions associated with EGFRis, it is likely that similar treatment approaches can be used as described above. However, prospective trials will be needed to better characterize these side effects, estimate their incidence, as well as to investigate potential management strategies.

Table 1: Characteristic, evolution and treatment of selumetinib associated dermatologic adverse effects

Patient	Age/Sex	Cutaneous toxicity	Onset of symptoms	Treatment	Resolution/Improvement
1	58/male	Papulopustular rash; pruritus; secondary superinfection;	On the 5 th day of therapy	Oral cephalexin 250 mg four times daily, topical mupirocin and triamcinolone 0.1% creams	Resolution in 1 month following discontinuation of selumetinib
2	53/female	Papular rash; xerosis; fissures	Within 2 weeks	Topical clindamycin phosphate 1%, clindamycin/benzoyl peroxide gel, pimecrolimus 1% cream; emollients	Significant improvement in 6 weeks while on selumetinib; Near complete resolution 6 weeks after discontinuation of selumetinib
3	51/female	Papulopustular rash; xerosis	On the 5 th day of therapy	Oral cephalexin, metronidazole cream	Resolution of the rash in approximately 10 weeks despite continued selumetinib treatment
4	52/female	Papulopustular rash; increased alopecia; paronychia; angular cheilitis; pruritus; telangiectasias; secondary superinfection	After 1 week of therapy	Topical triamcinolone 0.1% and mupirocin, oral cephalexin for papulopustular rash ¹	Significant improvement over 2 weeks following discontinuation of selumetinib; Complete resolution 4 months after discontinuation of therapy
5	76/male	Papulopustular rash; secondary superinfection; xerosis; pruritus hyperpigmentation	After 7 weeks of therapy	Oral cephalexin 250 mg four times a day, topical mupirocin, topical corticosteroids for xerosis	Significant improvement over 3 weeks while on selumetinib
6	52/Female	Papulopustular rash with crusted lesions involving the face	Within 2 weeks of therapy	Oral minocycline 100 mg a day and topical hydrocortisone cream twice a day	Significant improvement by 6th week with persistent maculopapular rash seen during 11th week of selumetinib treatment
7	59/Female	Papulopustular rash involving the face	Between 1st and 2nd week of treatment	No intervention	No follow up data
8	55/Female	Papulopustular rash involving the face	Between 1st and 2nd week of treatment	Topical metronidazole 0.5% cream and hydrocortisone 2.5% cream	Selumetinib was discontinued after 6 weeks; the rash mostly resolved within 3 weeks of discontinuing therapy
9	58/Male	Mildly pruritic papulopustular rash involving the scalp, face, chest, and upper back	After 5 days of treatment	Topical mupirocin and triamcinolone 0.1% creams twice a day. Fluocinolone solution for the scalp	Resolution in 1 to 2 weeks after discontinuing selumetinib
10	55/Male	Erythema, telangiectasias and pustules involving the nose	After 2 weeks of treatment	Topical alclometasone dipropionate 0.05% and oral minocycline 100 mg bid	Resolution within one month despite continued treatment with selumetinib

11	69/Male	Mildly pruritic papulopustular rash involving the upper chest, back and neck subsequently affecting the face and proximal extremities; Xerosis; Telangiectasias	Approximately 1 to 2 weeks after treatment	Topical fluocinonide and clindamycin with later addition of minocycline; 6% salicylic acid twice a day for xerosis	Improvement by 8 th week with persistent mild maculopapular rash seen 3 weeks after discontinuation of selumetinib.
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¹ For details on treatment of other toxicities, please refer to the text

Table 2. The spectrum of dermatologic toxicities associated with selumetinib

Dermatologic adverse effects	Patients affected, n (%)
Papulopustular rash	11 (100%)
Pruritus	5 (45%)
Xerosis cutis	4 (36%)
Secondary superinfection	3 (27%)
Telangiectasias	3 (27%)
Paronychia	1 (9%)
Hyperpigmentation	1 (9%)
Angular cheilitis	1 (9%)
Fissures	1 (9%)
Increased alopecia	1 (9%)

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Figures Legend:

Fig.1 Papulopustular rash affecting the face with lesions coalescing around the central aspect of the face.

Fig.2 Fissures of the heels

Fig. 3 Facial erythematous papules, particularly affecting the chin and cheeks

Fig. 4 Mild paronychia of the right thumb and dystrophic nail

Fig. 5 The skin biopsy shows parakeratosis, dermal edema and a predominantly perivascular inflammatory cell infiltrate

Fig. 6 The inflammatory cell infiltrate around and near small dermal vessels is predominantly composed of lymphocytes. Polymorphonuclear cells are also present, including eosinophils. The endothelial cells are swollen and there are nuclear fragments (karyorrhectic debris) as evidence of vascular damage.

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Figure 1

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Figure 1

Figure 2
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Figure 3

Figure 4

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Figure 4

Figure 5
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