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Granulomatous dermatitis as a postherpetic isotopic response in immunocompromised patients: A report of 5 cases

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Key words: Chronic lymphocytic leukemia; granuloma annulare; granulomatous dermatitis; immunocompromised district; immunodeficiency; immunocompromise; immunosuppression; isotopic response; locus minoris resistentiae; postherpetic isotopic response; Wolf's isotopic response.

INTRODUCTION

Granulomatous dermatitis (GD) describes disorders in which mixed inflammatory infiltrates composed primarily of histiocytes invade the skin. The pathogenesis of GD is unknown; however, GD has been noted to occur in areas previously affected by trauma, sun damage, or infection.[1] When GD presents at the same site of a healed, unrelated skin disease, it falls within the category of a Wolf's isotopic response.[2] The regional restriction of a Wolf's isotopic response is proposed to occur due to an area of localized immunocompromise known as an *immunocompromised district*.[3] This immunocompromised district is believed to result from various types of cutaneous damage that hinder lymph circulation, like chronic regional lymphedema or prior herpes virus infection (eg, varicella zoster virus [VZV] and herpes simplex virus [HSV]).[3] Postherpetic isotopic response (PHIR) is the most commonly reported isotopic response, and more cases of PHIR-GD have been reported than any other type of isotopic response.[3] It can occur within the same dermatomal distribution either immediately after primary lesion resolution (VZV>HSV) or many years later.[3] Persistent VZV DNA has been detected in PHIR lesions within 4 weeks after an acute episode[4,5] but not after 7 weeks.[6,7] The presence of viral DNA in some lesions has led to the proposal that VZV glycoproteins (gpI/II) may still be expressed at a sufficient level to initiate granuloma formation.[8]

Since the first report of granuloma annulare (GA) as an isotopic response,[9] 38% of the 32 cases have been reported in the setting of immunocompromise.[10] We now add 5 unreported cases and 16 literature cases (not reviewed in prior meta-analyses) of immunocompromised PHIR-GD. Our review of the literature has also added 23 cases of

Abbreviations used:

AML:	acute myelogenous leukemia
CLL:	chronic lymphocytic leukemia
GA:	granuloma annulare
GD:	granulomatous dermatitis
HSV:	herpes simplex virus
MM:	multiple myeloma
PHIR:	postherpetic isotopic response
PHIR-GD:	postherpetic isotopic response-granulomatous dermatitis
PHN:	postherpetic neuralgia
SCT:	stem cell transplant
SLE:	systemic lupus erythematous
SS:	Sjogren syndrome
VZV:	varicella zoster virus

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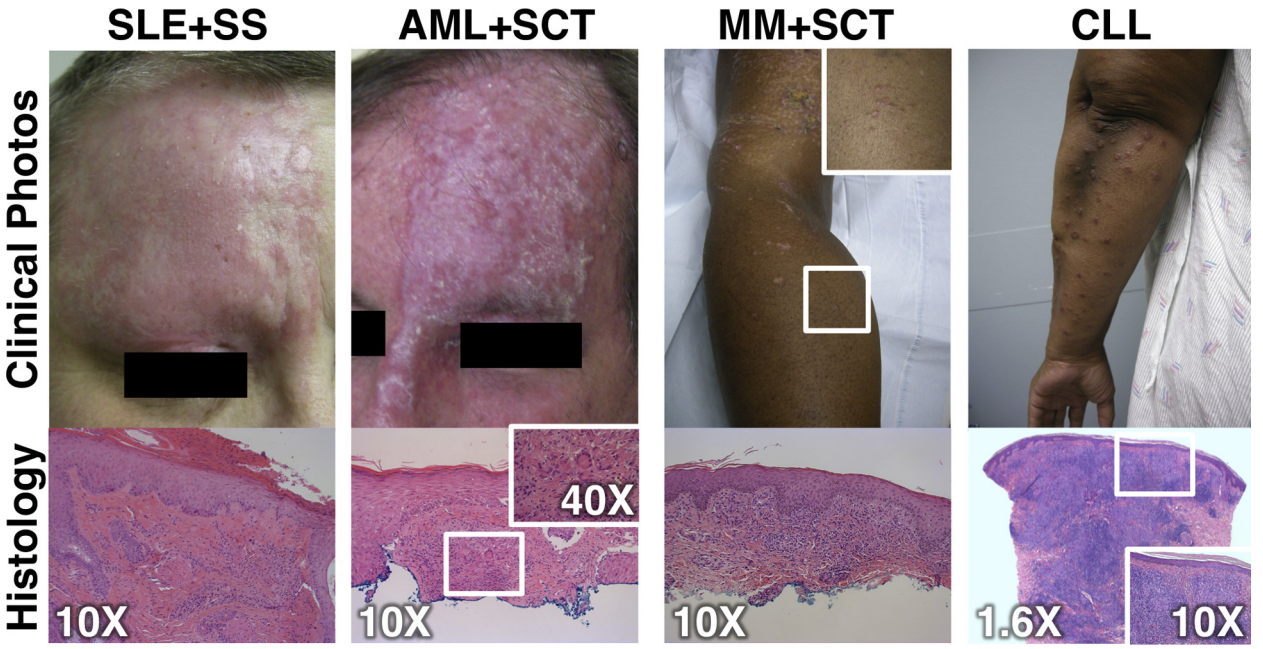

Fig 1. Clinical and histologic images. Four of the immunocompromised patients with granulomatous PHIR from this case series are shown with their clinical photographs above and the corresponding H&E pathology immediately below. Inset images show magnified areas of rash/histology. Immunocompromise etiology and microscopic magnifications are listed. No clinical/histologic images were available for the heart transplant subject in our case series.

nonimmunocompromised PHIR-GD. Our analysis of 33 immunocompromised and 43 immunocompetent cases highlights PHIR-GD associations with immunocompromise, chronic lymphocytic leukemia (CLL), and male sex.

METHODS

We conducted a retrospective study of 5 immunocompromised PHIR-GD patients at Barnes Jewish Hospital in St Louis, Missouri between 2008 and 2015. Through a literature search of PubMed, we reviewed all previous cases of PHIR-GD. Search terms included *Wolf's isotopic response*, *postherpetic isotopic response*, *granulomatous dermatitis*, *granuloma annulare*, and perturbations of these terms. References from the identified literature were used to expand our search.

RESULTS

Case 1

A 53-year-old white woman with systemic lupus erythematosus (SLE), Sjögren syndrome (SS), and IgM deficiency on methotrexate, Plaquenil, prednisone, and sulfasalazine presented with right V1 dermatome VZV reactivation. Treatment included valacyclovir, tobramycin ophthalmic ointment, and gabapentin. Less than a month after the lesions resolved, an erythematous, alopecic plaque appeared in the same dermatome (Fig 1; SLE+SS) complicated by severe postherpetic neuralgia (PHN) and trigeminal trophic syndrome with ulceration and superinfection (methicillin-resistant *Staphylococcus aureus*, *Candida* keratitis). Biopsy found no viral cytopathic changes (Fig 1; SLE+SS). HSV/VZV assays were negative. She received valacyclovir, corticosteroids (topical, intralesional, oral), and calcineurin inhibitors (tacrolimus, pimecrolimus) for her PHIR-GD. Her PHN required oral gabapentin, pregabalin, duloxetine, hydroxyzine, and topical lidocaine. Autoimmune treatments were replaced with abatacept 6 months after PHIR-GD onset. Over 19.5 months, her cutaneous disease and PHN significantly improved, but her PHN never resolved completely.

Case 2

A 56-year-old white man with a history of acute myelogenous leukemia (AML) treated with chemotherapy and unrelated donor stem cell transplant (SCT) later complicated by chronic graft-versus-host disease presented for suture removal after Mohs micrographic surgery for squamous cell carcinoma of the left side of the forehead. He was found to have VZV reactivation of the left V1 dermatome. He received intravenous acyclovir, oral valacyclovir, and gabapentin for PHN. Less than a month later, an erythematous, sclerotic plaque developed in the

same dermatome consistent with GD on biopsy (Fig 1; AML+SCT). He was treated topically (desonide, pimecrolimus) and orally (valacyclovir, prednisone, minocycline, dicloxacillin). PHIR-GD skin lesions and PHN persisted despite treatment at 1-year follow-up.

Case 3

A 57-year-old African-American woman with a history of multiple myeloma (MM) treated with chemotherapy followed by autologous SCT presented with right upper extremity (dermatomes C5-C6) VZV reactivation. She was treated with high-dose acyclovir. Two weeks later, flat-topped, violaceous, polygonal papules appeared among resolving VZV lesions (Fig 1; MM+SCT). Biopsy found poorly formed epithelioid granulomas in the superficial dermis with extension to the dermoepidermal junction and no lichenoid infiltrate or viral cytopathic change (Fig 1; MM+SCT). Grocott methenamine silver stain, and acid-fast bacilli stains were negative. PHIR-GD treatment (hydroxyzine, high potency topical steroids, intralesional Kenalog) resulted in significant improvement by 5 months. Complete resolution of cutaneous findings was noted at 2-year follow-up, although PHN persisted requiring gabapentin, topical lidocaine, and epidural steroid injections.

Case 4

A 73-year-old white man with a history of heart transplant in 1985 presented with disseminated VZV reactivation (right V3 and C5 dermatomes). At presentation, his immunosuppressive regimen included cyclosporine, azathioprine, and prednisone. VZV treatment included valacyclovir and gabapentin for PHN. Within 3 weeks, erythematous papules developed interspersed within his healing VZV lesions (right C5 dermatome) with significant PHN. VZV polymerase chain reaction was negative for both lesions. Biopsy found a prominent interstitial granulomatous process with necrobiosis and no viral cytopathic changes. Gram and Fite stains were negative. PHIR-GD was treated with clobetasol.

Case 5

A 71-year-old African-American woman with CLL complicated by immune thrombocytopenic purpura presented with VZV reactivation (left C5-T1 dermatomes) and significant PHN 1 month after rituximab treatment and ibrutinib initiation. She initially received valacyclovir, gabapentin, and acetaminophen-hydrocodone. Once the lesions resolved, she was treated with acyclovir prophylaxis. Eight months later, firm, erythematous papules in an annular pattern developed in a left-sided C5-8 distribution consistent with PHIR-GD (Fig 1; CLL). Biopsy found superficial and deep perivascular loose granulomas and lymphocytes (Fig 1; CLL). Gram, Grocott methenamine silver stain, and Fite stains were negative. Clobetasol cream improved her PHIR-GD by her follow-up at 4 months.

Summary of reported cases

These 5 cases were integrated into a review of all published immunocompromised PHIR-GD clinical and histologic data (Supplemental Figs 1 and 2). For comparison, PHIR granulomatous vasculitis and folliculitis cases were summarized separately (Supplemental Figs 3 and 4). The average age of PHIR-GD presentation was similar in immunocompromised patients (65 ± 11 years) and immunocompetent patients (59 ± 18 years). Although most PHIR-GD cases were initiated by VZV (>96%), HSV was identified in 9% of immunocompromised PHIR-GD cases. Similar to prior literature, herpes virus infection occurred on average 4.2 months before PHIR (range, 0.1 to 36), and most cases resolved within 1 to 2 years with conservative GD management, although our 5 new cases all were complicated by severe PHN.

Immunocompromise analysis

Immunocompromise in PHIR-GD appears more commonly (43%) than previously reported (38%) (Fig 2, *A*). We have expanded the previously identified immunocompromised context for PHIR-GD (chemotherapy or hematopoietic malignancy) to include HIV, myelodysplastic syndrome, solid organ transplant, and connective tissue disease (Fig 2, *B*). CLL remained the most common cause of immunocompromise in granulomatous PHIR patients (44% all cases/48% GD). Interestingly, our work suggests that sex may play a role in PHIR-GD, as immunocompromised men appeared particularly susceptible to granulomatous PHIR independent of their higher incidence of CLL (Fig 2, *C*). Conversely, granulomatous PHIR in immunocompetent patients is far more frequent in women (Fig 2, *C*) paralleling the increased occurrence of GA in women.[1]

DISCUSSION

Nearly half of PHIR-GD cases (33 of 76; 43%) have been reported in immunocompromised patients. Immunocompromise likely worsens the regional neuroimmune axis imbalance caused by herpetic nerve injury and thereby increases the likelihood of PHIR-GD.[11] This hypothesis is supported by recent PHIR-GD work demonstrating perineurovascular lymphohistiocytic infiltrates.[12] Further, the severe

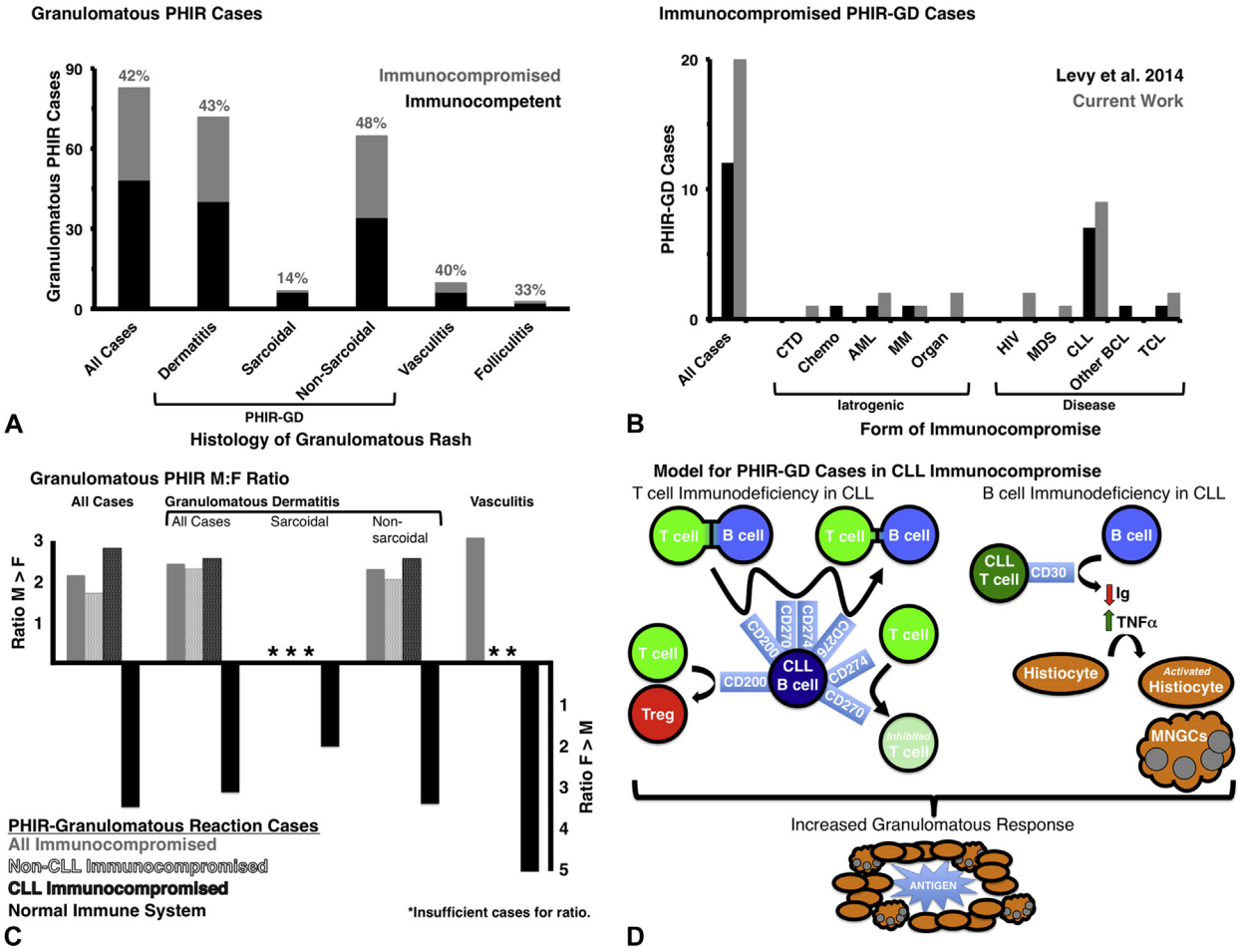

Fig 2. Immunocompromise and granulomatous PHIR. **A**, The presence or absence of immunocompromise in all published cases of granulomatous PHIR are summarized and separated by type of inflammation. PHIR-GD granulomatous dermatitis encompasses sarcoidal and nonsarcoidal (ie, GA and GA variants). **B**, Cases of PHIR-GD from the most recent meta-analysis before this publication are compared with the cases added by this work. The types of immunocompromise are listed and highlight the predominance of CLL in both studies. **C**, The male/female ratio for each type of granulomatous PHIR was calculated as a function of immunocompromise. Granulomatous PHIR folliculitis is not included, as there were too few cases to include in this analysis. **D**, Model of how CLL immunocompromise could lead to increased granulomatous response through both the T- and B-cell axes is shown. The upregulated CLL B-cell factors impair immunologic synapse formation, promote Treg expansion, and impair T cell activation/proliferation. Upregulated CLL T-cell CD30 impairs B-cell isotype switching, increases B-cell sensitivity to FasL-mediated apoptosis, and increases tumor necrosis factor-α production.

PHN of patients both in our study and prior publications may reflect this proposed neuroimmune imbalance. We recommend that practitioners aggressively manage these symptoms particularly in immunocompromised PHIR-GD patients. Beyond local neuroimmune effects, the overrepresentation of CLL in our PHIR-GD patients (16 of 33; 48%) compared with baseline CLL incidence (0.5%) may help illuminate what humoral and cell-mediated impairments led to granulomatous PHIR. The upregulation of specific cell surface proteins on adaptive immune cells (Fig 2, *D*),[13] immune cell-mediated hampered lymph drainage,[13] and increased tumor necrosis factor-α in CLL may help drive granuloma formation (Fig 2, *D*). Future studies of this phenomenon are needed to determine which facet(s) of CLL immunocompromise favors PHIR-GD, and we believe these studies will shed light on both PHIR (GD and other responses) and CLL. Although CLL association with PHIR-GD had been

previously noted, male predominance in immunocompromised PHIR-GD has not been previously identified. It is particularly striking because of the reported approximately 33% increased incidence of VZV in women over men[14] and the increased incidence of granuloma annulare in women over men (2.5:1),[1] which we also observed in our review of immunocompetent patients with PHIR-GD (2.9:1 overall, 2.6:1 for PHIR-GD). Although the male/female ratio in CLL (1.5:1) may account for part of the male predominance in PHIR-GD (2.8:1), it cannot account entirely for this observation. Although we do not yet understand the role of sex in PHIR-GD, we recommend screening men with PHIR-GD for immunocompromise (particularly CLL) and aggressively treating PHN in these patients to improve clinical outcomes. We hope that these cases and our literature review will spark future investigations to improve our understanding of PHIR, granulomatous reactions, and CLL.

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SI - TABLE I Immunosuppressed PHIR-GD – Clinical Summary

		REFERENCE	AGE	SEX	DISEASE	VIRUS	GRANULOMATOUS RASH[1] Time[2]	Antiviral	Immunosuppression Topical[4]	IL[5]	Oral[6]	Itch Oral	Pain Topical[7]	Oral[8]	Other	FOLLOW-UP Time[3]	Resolution
IATROGENIC	CTD	**McCoy**	53	F	SLE, SS[9]	VZV	< 1[10]	X	S,T,P	X	P	X	X	G,P,A,O	Antimicrobials[11]	19.5	Partial
	5FU	Levy	82	M	Cecal CA[12]	VZV	36			X	H,T						ILK only
	SCT	**McCoy**	56	M	AML	VZV	< 1	X	S,P		P,M			G	Dicloxacillin	16	Partial
		Wright*	68	M	AML	VZV	< 0.5									2	Complete
		McCoy	57	F	MM	VZV	< 0.5[13]		S	X		X	X	G,P,O		5	Complete
		Ezra	54	F	MM	VZV	1			X				G		1	Partial
		Sanli	46	M	Hodgkin's	VZV	4		S							0.75	Complete
	Solid	**McCoy***	73	M	Heart	VZV	< 1	X	S	X						2	None
		Vu	69	M	Renal	VZV	3		S							NR	Complete
VIRAL		Niedermeier	60	M	HIV	VZV	1.5[14]	X								NR	Less pain
		Nikkels	NR	NR	AIDS	VZV											
MDS		Watanabe	73	M	MDS	VZV	14	X	S							6	Complete
LEUKEMIA/LYMPHOMA	B-Cell	**McCoy**	71	F	CLL[15]	VZV	8		S		P			G,O		4	Partial
		Gibney	57	M	CLL	VZV	1	X								NR	Complete[16]
		Wright	62	F	CLL[17]	VZV	1	X			P					3	Partial
		Kapoor	64	M	CLL	VZV	2		S			X				2.5	Partial
		Winkelmann	67	F	CLL	VZV									ACTH	1	
		Pujol	68	M	CLL	VZV	0.75									1.5	Complete
		Zanolli*	71	M	CLL	VZV[18]	2.8		S								Complete
		Fischer*	71	M	CLL	VZV[19]	2									12	
		Jaka-Moreno	72	M	CLL	VZV	1		S								
		Sopenna	73	M	CLL	VZV	0.5									1.25	Complete
		Winkelmann	73	M	CLL	VZV		X									
		Gesierich	74	M	CLL	VZV		X									Complete
		Jaka-Moreno	79	F	CLL	HSV	0.5		S							NR	Complete
		Elgoweini	80	M	CLL	VAV	3									NR	Complete
		Wright	82	M	CLL	VZV	<1										
		Nikkels	NR	NR	CLL	VZV										1.75	
		Gibney	40	M	IBL	VZV	14	X									Complete[16]
	T-Cell	Krahl	51	F	Lennert	VZV	5		S							NR	
		Gutzmer	54	NR	T-cell NHL	VZV	0.5										
		Nikkels	NR	NR	AILD	HSV										1	

Abbreviations:
5FU = 5-FluoroUracil
AIDS = Acquired ImmunoDeficiency Syndrome
AILD = AngioImmunoblastic Lymphadenopathy with Dysproteinemia
AML = Acute Myelogenous Leukemia
CA = Cancer
CLL = Chronic Lymphocytic Leukemia
CTD = Connective Tissue Disease
F = Female
HSV = Herpes Simplex Virus
IBL = ImmunoBlastic lymphoma
M = Male
MM = Multiple Myeloma
MDS = Myelodysplastic syndrome
NHL = non-Hodgkin lymphoma
NR = Not Recorded
SCT = Stem Cell Transplant
SLE = Systemic Lupus Erythematosus
SS = Sjogren's Syndrome
VZV = Varicella Zoster Virus

Type of immunocompromise is listed on left. Studies identified by Levy et al. (2014). *All cases were dermatomal except 3 generalized cases. [1]All viral rashes treated with antivirals. [2]Time in months between viral and granulomatous rashes. [3]Time in months. [4]S/T/P = Steroid/Tacrolimus/Pimecrolimus. [5]IL = IntraLesional steroid (5-10 mg/ml). [6]H/M/P/T = Hydroxychloroquine/Minocycline/Prednisone/Trental(Pentoxifylline). [7]Topical lidocaine (patch/gel/both). [8]G/P/A/O = Gabapentin/Pregabalin/Antidepressant/Opiod. [9]Patient also had IgM deficiency. [10]May have been as short as <1 week. [11]Ulcer and secondary infection (MRSA, Candida) treated with mupirocin, vancomycin, voriconazole, natamycin drops, and doxycycline. [12]Also had diabetes mellitus type 2. [13]GD began while VZV crusted lesions were present and pruritic, but primary VZV rash had resolved with treatment. [14]Somewhat unclear if VZV had resolved prior to GD. [15]Complicated by ITP treated with ibrutinib. [16]No improvement with antiviral, but lesions self-resolved over 3 months. [17]Status post rituximab, also with concurrent breast cancer. [18]May have been primary varicella or HSV. [19]May have been primary varicella.

Supplemental Fig 1. Clinical summary of immunosuppressed PHIR-GD cases. Clinical data including patient characteristics, immunosuppression, virus, and treatment for all reported cases of PHIR-GD and the 5 cases reported in this manuscript are summarized.

SI - TABLE II Immunosuppressed PHIR-GD – Histology

		REFERENCE	AGE	SEX	DISEASE	GRANULOMA Type	Pattern	Area[4]	MNGCs[5]	Necro[6]	Mucin	Lymphs	VIRAL WORK-UP[1] Tzanck	Cx	PCR	EM	IHC	INFXN[2]	DX[3]
IATROGENIC	CTD	**McCoy**	53	F	SLE, SS[7]														GD
	5FU	Levy	82	M	Cecal CA[8]		Interstitial		X										GA
	Transplant SCT	**McCoy**	56	M	AML														GD
		Wright*	68	M	AML	Epithelioid											NO	G/F/Fite	GD
		McCoy	57	F	MM	Epithelioid		DEJ,SD										F/A	GD
		Ezra	54	F	MM		Palisading	SD	X		X	X						F/A	GA
		Sanli	46	M	Hodgkin's	Epithelioid	Palisading		X	X									GA
	Solid	**McCoy**	73	M	Heart		Interstitial			X								F/Fite	GA
		Vu	69	M	Renal			Dermis				X		NO				F/A	GD
VIRAL		Niedermeier	60	M	HIV			PF	X			X			YES				*
		Nikkels	NR	NR	AIDS			M/DD,PV									YES		GD
MDS		Watanabe	73	M	MDS	Sarcoidal		S/DD	X						NO			F	SG
LEUKEMIA/LYMPHOMA	B-Cell	**McCoy**	71	F	CLL[9]		*Loose*	S/DPV				X						G/F/A/Fite	GD
		Gibney	57	M	CLL		Palisading	S/DD	X			X			YES				GD
		Wright	62	F	CLL[10]	Epithelioid	*Discohesive*		X								NO	G/F/Fite	GD
		Kapoor	64	M	CLL			PN,PF	X[11]		X	X			NO		NO	All	GA
		Winkelmann	67	F	CLL														GA
		Pujol	68	M	CLL	Epithelioid		S/MD	X							NO	NO	G/F/A	GD
		Zanolli*	71	M	CLL		Palisading	PV,IN	X				YES						GA
		Fischer*	71	M	CLL	Epith/Tuber[12]		Dermis	X			X						F/A/Fite	TGA
		Jaka-Moreno	72	M	CLL			PV,IN				X							GD
		Sopenaa	73	M	CLL	Epith/Tuber[12]			X									G/F/A	GD/GF
		Winkelmann	73	M	CLL														GA,GV
		Gesierich	74	M	CLL				X						YES				GD
		Jaka-Moreno	79	F	CLL		*Poorly def*[13]	SD	X			X					NO		GD
		Elgoweini	80	M	CLL		Interstitial					X							GV
		Wright	82	M	CLL		*Loose*	SD	X			X						F/A	SGA
		Nikkels	NR	NR	CLL			M/DD,PV									YES		GD
		Gibney	40	M	IBL		Palisading	Dermis	X			X			NO				GD
	T-Cell	Krahl	51	F	Lennert														PGA
		Gutzmer	54	NR	T-cell NHL										YES				
		Nikkels	NR	NR	AILD			M/DD,PV									YES		GD

Form of immunosuppression is listed on left. Information that is not listed was not available. Terms in *ITALICS* are non-standard pathological descriptors. Studies identified by Levy et al. (2014) are underlined. [1]Assays used to evaluate for presence of Herpes virus during PHIR. YES/NO indicates presence/absence of viral readout. [2]Infectious work-up. Gram (G); Fungi (F) - Grocott's methenamine silver or periodic acid-schiff (PAS); Acid fast bacilli (A); Fite; All = G/F/A/Fite. All reported studies were negative. [3]Diagnosis assigned by author: Granuloma Annulare (GA), Granulomatous Dermatitis (GD), Granulomatous Vasculitis (GV), Perforating GA (PGA), Sarcoidal Granulomas (SG), Sarcoidal GA (SGA), Tuberculoid GA (TGA). *Granulomatous plaque type herpes zoster. [4]Infiltrate localizations: Dermal-Epidermal Junction (DEJ), Superficial/Mid/Deep Dermis (S/M/DD), INterstitial (IN), PeriFollicular(PF), Superficial/Deep PeriVascular(S/DPV), PeriNeural(PN). [5]MNGCs = Multi-Nucleated Giant Cells. [6]Necrobiosis. [7]Patient also had IgM deficiency. Biopsy showed ulcer but clinical was consistent with granulomatous process. [8]Also had diabetes mellitus type 2. [9]Complicated by ITP. [10]Status post rituximab, also had breast cancer. [11]Some with elastophagocytosis. [12]Mix of epithelioid/tuberculoid pattern. [13]Poorly defined pattern. Abbreviations (see TABLE I).

Supplemental Fig 2. Histologic summary of immunosuppressed PHIR-GD cases. Patient characteristics (age, sex, immunosuppression) are listed next to available histologic data for all reported cases of PHIR-GD and the 5 cases reported in this manuscript.

SI - TABLE III PHIR-GV/GF – Clinical Summary

	REFERENCE	AGE	SEX	DISEASE[1]	VIRUS	GRANULOMATOUS RASH[1] Time[2]	Antiviral	Immunosuppression Topical[4]	IL[5]	Oral[6]	Itch Oral	Pain Topical[7]	Oral[8]	Other	FOLLOW-UP Time[3]	Resolution
Folliculitis	Requena	78	F		VZV	1.8										
	Schena	52	F		VZV		X							Emollients		Complete
	Fernández-Redondo	58	F	CTCL	VZV	1	X								~1	Complete
	Sopenna	73	M	CLL	VZV	0.5									1.25	Complete
Vasculitis	Requena	57	M		VZV	1.8										
	Requena	65	F		VZV	2									~1	Complete
	Rodríguez-Pereira	72	F		VZV	1.8									NA	
	Snow	65	F		VZV			S				C	A	CBZ,NB	1	Partial
	Snow	66	F		HSV	0.5	X			P					1	Complete[9]
	Snow	76	F		HSV		X								2	Partial
	Baalbaki & Malak	59	F	Gastric CA	VZV	0.75				P			A	CBZ		
	Langenberg	27	M	HIV	VZV	5	X	S							~1	Complete
	Winkelmann*	73	M	CLL	VZV											
	Elgoweini	80	M	SLL	VZV										10	Complete

Abbreviations:
CA = Cancer
CBZ = CarBamaZepine
CLL = Chronic Lymphocytic Leukemia
CTCL = Cutaneous T Cell Lymphoma
F = Female
HSV = Herpes Simplex Virus
M = Male
NB = Nerve Block.
VZV = Varicella Zoster Virus

Histology is listed on left. Information that is not listed was not available. [1]All viral rashes initially treated with antivirals and all presentations were dermatomal. Treatments refer to PHIR treatment. [2]Time in months between viral rash and granulomatous rash. [3]Time in months. [4]S/T/P = Steroid/Tacrolimus/Pimecrolimus. [5]IL = IntraLesional steroid (5-10 mg/ml). [6]H/M/P/T = Hydroxychloroquine/Minocycline/Prednisone/Trental(Pentoxifylline). [7]L/C = Lidocaine (patch/gel/both)/Capsaicin. [8]G/P/A/O = Gabapentin/Pregabalin/Antidepressant/Opiod. [9]Recurred without antiviral prophylaxis.

Supplemental Fig 3. Clinical summary of immunosuppressed PHIR-GV/GF cases. Clinical data including patient characteristics, immunosuppression, virus, and treatment for all reported cases of PHIR-GV/GF (granulomatous vasculitis/folliculitis) are summarized.

SI - TABLE IV PHIR-GF/GV – Histology

	REFERENCE	AGE	SEX	DISEASE[1]	GRANULOMA							VIRAL WORK-UP[1]					INFXN[2]	DX[3]
					Type	Pattern	Area[4]	MNGCs[5]	Necro[6]	Mucin	Lymphs	Tzanck	Cx	PCR	EM	IHC		
Folliculitis	Requena	78	F						xxx					NO		xxx		GF
	Schena	52	F				PF				xxx	xxx			xxx			GF
	Fernández-Redondo	58	F	CTCL			SD,PF	X										GF
	Sopenna	73	M	CLL	Epith/Tuber[7]			X		xx							G/F/A	GD/GF
	Requena	57	M											NO				GV
	Requena	65	F				SD,DPV						NO	NO				GV
	Rodríguez-Pereira	72	F		Epithelioid		SD,S/DPV	X						NO			F/A	GV
	Snow	65	F				PV						NO	NO				GV
	Snow	66	F			*Poorly def*[8]	S/MD,SPV	X						YES				GV
	Snow	76	F				SD,SPV							YES				GV
Vasculitis	Baalbaki & Malak	59	F	Gastric CA			D,SC										F/A/Fite	GV
	Langenberg	27	M	HIV		*Loose*	SD,PV							NO			F/A	GV
	Winkelmann*	73	M	CLL														
	Elgoweini	80	M	SLL		Interstitial	PV											GV

Histology is listed on left. Information that is not listed was not available. Terms in *ITALICS* are non-standard pathological descriptors. [1]Assays used to evaluate for presence of Herpes virus during PHIR. YES/NO indicates presence/absence of viral readout. [2]Infectious work-up. Gram (G); Fungi (F) - Grocott's methenamine silver or periodic acid-schiff (PAS); Acid fast bacilli (A); Fite; All = G/F/A/Fite. All reported studies were negative. [3]Diagnosis assigned by author: Granulomatous Folliculitis (GF), Granulomatous Dermatitis (GD), Granulomatous Vasculitis (GV). [4]Infiltrate localizations: Superficial/Mid/Deep Dermis (S/M/DD), PeriFollicular(PF), SubCutaneous(SC), Superficial/Deep PeriVascular(S/DPV). [5]MNGCs = Multi-Nucleated Giant Cells. [6]Necrobiosis. [7]Mix of epithelioid/tuberculoid pattern. [8]Poorly defined pattern. Other abbreviations (see TABLE III).

Supplemental Fig 4. Histologic summary of immunosuppressed PHIR-GF/GV cases**.** Patient characteristics (age, sex, immunosuppression) are listed next to available histologic data for all reported cases of PHIR-GF/GV.