Medical Mystery Case: The Over Exposure

PODCAST 47

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Learning Objectives

1. Assess real-life challenges with HSV/VZV diagnosis.
2. Integrate information on lesion analysis and improved diagnostic techniques.
3. Identify and describe benefits of multiplex testing to improve outcomes.

Disclosures

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The Over Exposure

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Our patient, Andre, presented with genital lesions after a photography trip to an African wildlife preserve.

Dr. Johnson had a wide variety of differentials to consider….

Many pathogens and non-pathogenic etiologies may lead to cutaneous, oral, or genital lesions

Lesion-Causing Etiologies	
HSV-1/HSV-2	VZV
Mpox (monkeypox)	Psoriasis
Syphilis	Cellulitis
Chancroid	Insect bites
Lymphogranuloma venereum (LGV)	Dermatitis
Granuloma inguinale (donovanosis)	Folliculitis
Fungal/yeast infections	Ecthyma
Crohn’s disease	Cnidaria envenomation
Behçet's syndrome	Contact stomatitis
Fixed drug eruptions	Lichen striatus

Roett M. *Am Fam Physician*. 2020;101(6):355-361.
Wilms L, et al. *JDDG*. 2022;20(10):1327-1351.

Why did Dr. Johnson think of testing Andre for HSV first?

- Andre had unprotected sex with a woman in Africa during his trip.
- Rates of genital lesions and genital ulcer disease (GUD) vary by pathogen, population, age, and geographic location.
- Herpes simplex virus (HSV) is one of the most common causes of GUD.
- In 2016 alone, 187 million people globally, or 5% of the world's population, had at least one episode of HSV-related GUD.

Loh AJW, et al. *Front Med (Lausanne)*. 2022;8:806605.

Herpes simplex (HSV)

- HSV-1 most commonly affects skin and oral mucous membranes, while HSV-2 lesions are seen in genital mucous membranes – but both can appear anywhere on the body.
- As a result of oral-to-genital contact, there is an increasing prevalence of HSV-1 in genital lesions and HSV-2 in oral lesions.
- Over 66% of individuals under 50 have HSV-1.
- HSV-2 is one of the most common sexually transmitted infections with up to 90% of infections unrecognized and undiagnosed.

Wilms L, et al. *JDDG*. 2022;20(10):1327-1351.
Saleh D, Yarrarapu SNS, Sharma S. Herpes Simplex Type 1. [Updated 2023 August 28]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482197/. Accessed January 6, 2025.
Mathew Jr J, Sapra A. Herpes Simplex Type 2. [Updated 2024 March 13]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554427/. Accessed January 6, 2025..

Why did Dr. Johnson also consider VZV and herpes zoster?

- Andre had varicella infection (chickenpox) as a child and had not had the shingles vaccine.

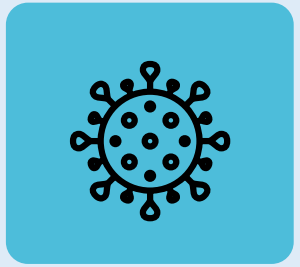
Lesion-causing varicella zoster (VZV)

- VZV is known for causing cutaneous lesions in chickenpox and herpes zoster (shingles).
- More than 95% of the adult world population is infected with latent VZV.
- 50% of those unvaccinated may develop herpes zoster by 85 years of age.
- Early diagnosis and treatment can shorten zoster duration and may reduce the risk of chronic complications.

Nagel MA, Gilden D. *Curr Opin Neurol*. 2014;27(3):356-60.
Gruver C, Guthmiller KB. Postherpetic Neuralgia. [Updated 2023 Apr 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK493198/. Accessed October 15, 2023.

Similar clinical presentations of HSV, VZV, and other lesion-causing pathogens impact diagnosis

Visual differentiation is not possible for most lesion-causing pathogens.



Atypical presentations are difficult to distinguish.

- Lesions in genital dermatomes
- Immunocompromised patients

The only way to definitively determine a diagnosis for HSV or herpes zoster is through laboratory testing.

Wilms L, et al. *JDDG*. 2022;20(10):1327-1351.

Cutaneous HSV and herpes zoster can be indistinguishable upon visual examination and can differ by skin tone

Herpes Simplex

- Clusters of vesicles on an erythematous base
- Progress to pustules and ulcerations over several days

Herpes Zoster

- Clusters of erythematous papules
- Progress to ulcerated vesicles over several days

Erythema may be reduced or appear violaceous or brown in skin of color.

Dermatology Atlas. Herpes simplex. http://www.atlasdermatologico.com.br/disease.jsf?diseaseId=182. Accessed July 10, 2024.
Dermatology Atlas. Herpes zoster. http://www.atlasdermatologico.com.br/disease.jsf?diseaseId=183. Accessed July 10, 2024.
DermNet. https://dermnetnz.org/cme/viral-infections/herpes-zoster-cme. Accessed July 10, 2024.
Saleh D, Yarrarapu SNS, Sharma S. Herpes Simplex Type 1. [Updated 2023 Jul 24]. https://www.ncbi.nlm.nih.gov/books/NBK482197/. Accessed October 15, 2023.
Mathew Jr J, Sapra A. Herpes Simplex Type 2. [Updated 2023 Aug 7]. https://www.ncbi.nlm.nih.gov/books/NBK554427/. Accessed October 15, 2023.
Adawi W, et al. *Dermatol Clin*. 2023;41(3):417-429.

OMG Quiz

Three patients have presented at urgent care with lesions at different anatomical locations.

All report recent unprotected sex with new partners.

None report fever or other systemic symptoms.

Can you diagnose these patients visually?

OMG Quiz: How would you diagnose these three patients?

?

?

?

Dermatology Atlas. http://www.atlasdermatologico.com.br/disease.jsf?diseaseId=182. Accessed April 28, 2024.
Public Health Image Library. https://phil.cdc.gov. Accessed April 28, 2024.

OMG Quiz: Did you get it right?

HSV

Herpes zoster

Primary syphilis

Dermatology Atlas. http://www.atlasdermatologico.com.br/disease.jsf?diseaseId=182. Accessed April 28, 2024.
Public Health Image Library. https://phil.cdc.gov. Accessed April 28, 2024.

Similarities and differences between HSV & zoster lesions

	Herpes zoster	HSV-1	HSV-2
Clinical presentation (Primary)	• Clustered blister lesions • Vesicles may progress to pustules with umbilication and scabs	• Clustered vesicles on an erythematous base • Vesicles may progress to pustules and ulcerations	• Clusters of macular or papular lesions • Vesicles may progress to pustules and ulcerations
Clinical presentation (Recurrence)	• Grouped papules become ulcerated vesicles • 1-2 contiguous dermatomes • Lesions may be painful	• Recurrent lesions may be milder	• Same grouped presentation as primary lesions • Lesions may be painful
Duration	• Chickenpox: 4-7 days • Zoster: 2-4 weeks	18.8 ± 6.5 days	21.5 ± 6.8 days
Average time to recurrence	Years	> 6 months	~ 80 days
Average recurrences/year	> 1	0.24	3.9
Primary shedding	Yes	15%	85%
Recurrence shedding	Yes	2%	98%

Gruver C, Guthmiller KB. Postherpetic Neuralgia. https://www.ncbi.nlm.nih.gov/books/NBK493198/. Accessed October 15, 2023.
Saleh D, Yarrarapu SNS, Sharma S. Herpes Simplex Type 1. [Updated 2023 Jul 24]. https://www.ncbi.nlm.nih.gov/books/NBK482197/. Accessed October 15, 2023.
Mathew Jr J, Sapra A. Herpes Simplex Type 2. [Updated 2023 Aug 7]. https://www.ncbi.nlm.nih.gov/books/NBK554427/. Accessed October 15, 2023.
Ayoade F, Kumar S. Varicella-Zoster Virus (Chickenpox) [Updated 2022 Oct 15]. https://www.ncbi.nlm.nih.gov/books/NBK448191/. Accessed October 15, 2023.
Hook EW. *Med Lab Obs*. 2012;44(7):8-12.

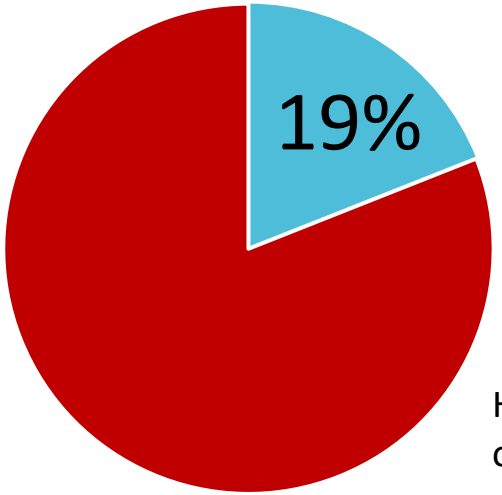
Why didn’t Dr. Johnson use syndromic management for HSV?

- Sensitivity of syndromic management to diagnose HSV is only 43.5%, while specificity is 88%.

Loh AJW, et al. *Front Med (Lausanne)*. 2022;8:806605.

Clinical diagnosis of herpes zoster may need to rule out HSV

VZV Differential Diagnosis[1]	
HSV	Insect bites
Impetigo	Papular urticaria
Contact dermatitis	Candida
Folliculitis	Dermatitis herpetiformis
Scabies	Drug eruptions

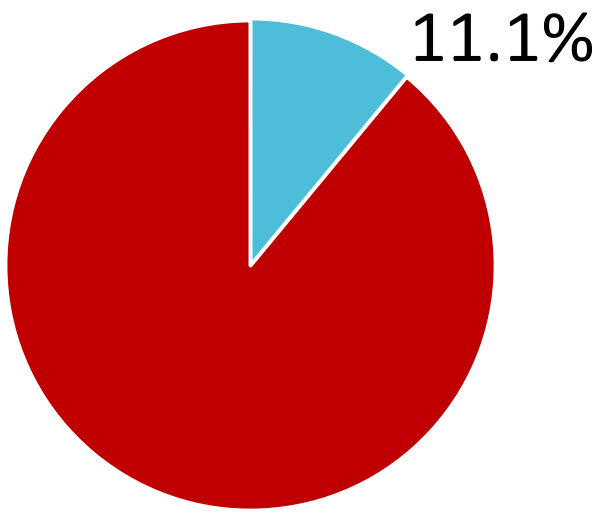


HSV is found over 19% of suspected typical herpes zoster cases.[2]

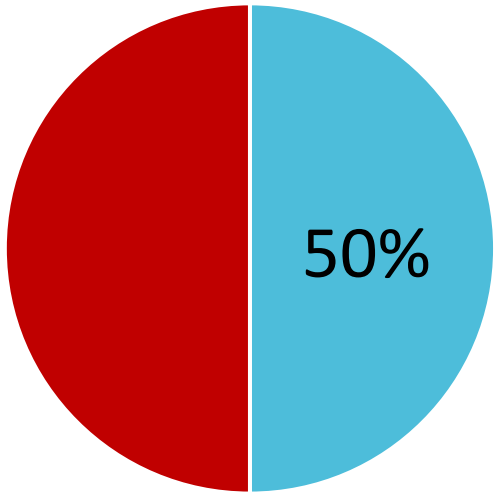
- Dermatome distribution of herpes zoster may be distinctive enough to make an accurate clinical diagnosis.[1]
- HSV is the primary differential diagnosis for herpes zoster, particularly when the face and genital region are affected.[2]
- Molecular assays frequently find HSV in patients with suspected herpes zoster.[2]

1. Centers for Disease Control. Shingles (Herpes Zoster) Diagnostic Testing. https://www.cdc.gov/shingles/hcp/diagnosis-testing.html. Accessed October 20, 2023.
2. Nikolic D, et al. *Am J Clin Pathol.* 2019;151(1):122–126.

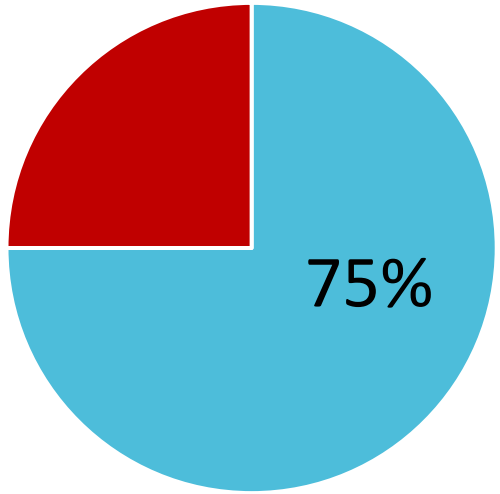
VZV is frequently detected in suspected HSV



VZV is found in over 11% of suspected HSV cases.



50% of these cases are in genital regions.



75% are not suspected to be herpes zoster due to presentation.

Most frequent misdiagnosis occurs in facial and genital regions.

Nikolic D, et al. *Am J Clin Pathol.* 2019;151(1):122–126.
Granato PA, et al. *J Clin Virol*. 2016;84:87-89.

What do the guidelines say about testing for HSV and herpes zoster?

CDC STI treatment guidelines recommend molecular testing

> Clinical diagnosis of genital herpes can be difficult because the self-limited, recurrent, painful, and vesicular or ulcerative lesions classically associated with HSV are absent in many infected persons at the time of clinical evaluation.

If genital lesions are present, clinical diagnosis of genital herpes should be confirmed by type-specific virologic testing from the lesion by NAAT or culture.

https://www.cdc.gov/std/treatment-guidelines/herpes.htm

EU guidelines for the management of genital herpes suggests herpes zoster testing for atypical lesions

- Clinical diagnosis alone should be avoided.
- The majority of patients will suffer from atypical lesions.
- **Herpes zoster molecular tests should be performed if genital manifestations are not clearly typical of HSV.**

- Molecular detection is the gold standard viral antigen detection is no longer recommended except in extremely limited resource settings.
- HSV typing into HSV-1 and HSV-2 is recommended in all patients with first-episode genital herpes to guide counselling and management.

Patel R, et al. *J Eur Acad Dermatol Venereol.* 2024 Dec 2. doi: 10.1111/jdv.20450. Epub ahead of print.

Both HSV and herpes zoster can be treated with some of the same antivirals.

Why was it important for Dr. Johnson to differentiate?

HSV and herpes zoster treatment efficacy depends on timely diagnosis

HSV and herpes zoster have different treatments for primary outbreaks, recurrences, and viral suppression. Dosages differ depending on viral type, outbreak severity, and health status of the patient.

	HSV-1	HSV-2	VZV (Chickenpox)	VZV (Zoster)
Initial outbreak	• Acyclovir* • Famciclovir • Valacyclovir	• Acyclovir* • Famciclovir • Valacyclovir	• Oral or IV acyclovir if at risk for moderate to severe disease or immunocompromised	• Acyclovir • Valacyclovir • Famciclovir • Brivudin
Recurrence	As needed	Episodic recurrences and viral suppression • Acyclovir* • Famciclovir • Valacyclovir	None	• Acyclovir • Famciclovir • Consider vaccination if over 50 or immunocompromised
Most effective treatment window	24 hours	24 hours	24 hours	72 hours

* In unresponsive cases, resistance should be considered. Foscarnet or cidofovir are alternatives for acyclovir resistance.

1. https://www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540242/all/Herpes_Simplex_Virus. Accessed November 1, 2023.
2. https://www.cdc.gov/std/treatment-guidelines/herpes.htm. Accessed November 1, 2023.
3. https://wwwnc.cdc.gov/travel/yellowbook/2024/infections-diseases/varicella-chickenpox#treatment. Accessed November 1, 2023.
4. https://www.cdc.gov/shingles/5-things-you-should-know.html. Accessed November 1, 2023.
5. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8876683/. Accessed November 1, 2023.

Why did Dr. Johnson choose a multiplex molecular test?

Multiplex molecular testing with HSV & VZV perform better than culture and DFA

	Simplexa HSV 1&2 Direct (Diasorin)	Simplexa VZV Swab Direct (Diasorin)	Savanna HSV 1&2 + VZV (QuidelOrtho)	Solana HSV 1&2 + VZV (QuidelOrtho)
	~60 Mins	~60 Mins	~24 Mins	50 Mins
HSV 1 Sensitivity (%)	98.8		99.1	100
HSV 1 Specificity (%)	97.6		97.6	97.0
HSV 2 Sensitivity (%)	99.3		96.4	98.0
HSV 2 Specificity (%)	97.6		99.4	96.3
VZV Sensitivity (%)		98.0	100	100
VZV Specificity (%)		99.2	99.9	97.3

	HSV Culture	VZV DFA
HSV Sensitivity (%)	71.1	NA
HSV Specificity (%)	93.2	NA
VZV Sensitivity (%)	NA	71.4
VZV Specificity (%)	NA	100

Nikolic D, et al. *Am J Clin Pathol.* 2019;151(1):122–126.
Package Insert. Simplexa HSV 1&2 Direct. Diasorin
Package Insert. Simplexa VZV Swab Direct. Diasorin
Package Insert. Savanna HSV 1+2/VZV. QuidelOrtho
Package Insert. Solana HSV 1+2/VZV. QuidelOrtho

Summary

- There are substantial challenges in diagnosing cutaneous and mucocutaneous lesions.
- Guidelines suggest molecular testing when available and studies note that syndromic management, DFA, and culture are not as sensitive and specific for the diagnosis of HSV and herpes zoster.
- Availability of multiplex molecular lesion testing could improve time to results and address disparities associated with visual diagnosis for some patients.

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