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CASE REPORT

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Multifocal osteomyelitis in a child with sickle cell disease and review of the literature regarding best diagnostic approach

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Key Clinical Message: In patients with sickle cell disease, we must be more cognizant of the possibility of multifocal osteomyelitis. Diagnosis can be challenging in this patient population as the symptoms mimic vaso-occlusive crisis. There is no gold standard in imaging.

Abstract: Osteomyelitis occurs more frequently in children with sickle cell disease. Diagnosis is challenging as it mimics vaso-occlusive crises, a common manifestation of sickle cell disease. We present a case of a 22-month-old girl with sickle cell disease and multifocal osteomyelitis. We review the literature on the utility of diagnostic imaging.

KEYWORDS

bacteremia, diagnostic approach, literature review, multifocal osteomyelitis, sickle cell disease

1 | INTRODUCTION

Osteomyelitis is a dangerous infection that can occur with higher propensity in patients with sickle cell disease. It can be challenging to diagnosis osteomyelitis in this population, as the clinical presentation can be mistaken for a vaso-occlusive crisis. Many of the symptoms, fever, tenderness in the extremity, swelling and decreased range of motion can be symptoms to both disease.[1] Osteomyelitis is also often missed, as vaso-occlusive crisis is much more common than osteomyelitis, and is considered the most common manifestation of sickle cell disease in children.[1] There is not a laboratory test or imaging modality that directly differentiates between these conditions. However, it is essential to determine the correct diagnosis, as missing osteomyelitis can have many dangerous implications, including chronic osteomyelitis, bone deformities, and sepsis.[1] Further investigation into the most accurate and efficient imaging for multifocal osteomyelitis must be performed, as there may be utility in whole-body MRI or PET scans. We present a case of a 22-month-old girl with sickle cell disease who developed salmonella bacteremia and multifocal osteomyelitis, and we review the literature on the utility of different imaging studies for this diagnosis.

2 | CASE DESCRIPTION

A 22-month-old female with sickle cell disease, type SS, presented to the Emergency Department with 3 days of left foot pain and swelling and 1 day of refusal to ambulate. Parents denied erythema, fever or trauma. The patient was afebrile with mild tachycardia, but non-toxic appearing. She had bilateral swelling of her feet and toes, with tenderness, palpation, and greater swelling of the left foot. Both extremities were warm and well perfused with

intact sensation. Laboratory evaluations were remarkable for leukocytosis with white blood cell (WBC) count of 18.4×10E9/L (6.0–17.5), anemia with a hemoglobin of 6.8 g/dL (10.5–13.5) and C-reactive protein (CRP) of 29.77 mg/dL (<1.00). X-rays did not show fracture, dislocation or other abnormalities. The patient was admitted for pain control for a vaso-occlusive pain crisis. Figure 1 shows a timeline for the patient's hospital course.

2.1 | Timeline

See Figure 1.

2.2 | Diagnostic assessment

Once hospitalized, the patient spiked a fever to 39.3 degrees Celsius and was started on Ceftriaxone. She received pain medications and a packed red blood cell transfusion.

The patient continued to be febrile and tachycardic on the second day of admission. Her blood culture was positive for gram negative bacilli at 25 h, speciated as Salmonella. Inflammatory markers showed Erythrocyte Sedimentation rate (ESR) of 23 mm/h and CRP of 35 mg/dL. The differential diagnosis was broadened to osteomyelitis versus septic joint versus bony abscess. Orthopedics was consulted and aspiration of fluid from the left ankle joint showed a cell count of 9710/μL with 85% polymorphic neutrophils and gram stain with 1+ gram positive cocci. Vancomycin was added to her antimicrobial regimen. MRI showed osteomyelitis of the left calcaneus, the outer cuneiform and the tibial diaphysis. A large plantar soft tissue abscess from the calcaneus anteriorly to the forefoot was also noted. An additional abscess was seen lateral to the calcaneal body between the calcaneus and the fibula. The patient ultimately went to the Operating Room (OR) for irrigation and debridement of the left ankle joint and left foot plantar abscess. Intra-operative cultures grew pan-susceptible Salmonella species.

On day 7 of hospitalization the patient's fever curve worsened and she developed right hand swelling. PET-CT showed multifocal areas of hypermetabolism in the right foot and hand, concerning for additional foci of osteomyelitis. The PET image is shown in Figure 2. Laboratory evaluations continued to show leukocytosis, now with WBC of 21×10 E9/L and CRP of 19 mg/dL. After the PET-CT results, orthopedics re-evaluated the patient and recommended only medical management.

On day 11, there was concern for increased fluctuance over the left foot. Repeat left foot MRI showed increased signal in the left calcaneus and lateral cuneiform. Additional MRIs of the right hand showed multifocal sites concerning for osteomyelitis and a subperiosteal abscess in the 4th metacarpal, but no significant fluid collection. The right foot MRI was concerning for osteomyelitis of the tibial diaphysis, 1st and 3rd metatarsal and lateral cuneiform. The patient underwent repeat left ankle incision and drainage with left calcaneus and lateral cuneiform drilling.

Our patient improved clinically after two surgical interventions. Her CRP decreased to 1.45 mg/dL by hospital day 20. She completed a 14-day course of Ceftriaxone and was then switched to oral Amoxicillin for a total of 6 weeks of antibiotics. Her total hospitalization was 29 days. The patient was observed closely post hospitalization, continued to recover well and completed her antibiotic course without any issues. She has not had any more recurrences of osteomyelitis or other serious infections to date.

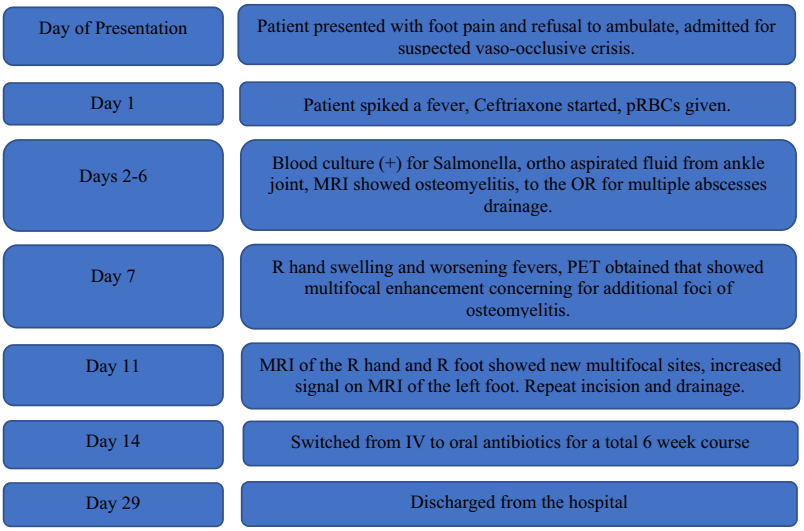

FIGURE 1 Hospital course for the patient.

FIGURE 2 PET image of patient.

3 | DISCUSSION

The most common acute manifestation of sickle cell disease in the pediatric population is a vaso-occlusive crisis.[1] Osteomyelitis is an infection of the bone that occurs with higher propensity in patients with sickle cell disease due to impaired immune function and functional asplenia.[1] As in our case, it is often challenging to diagnose osteomyelitis in children with sickle cell disease, as the presenting symptoms are often mistaken for a vaso-occlusive crisis. These symptoms often include fever, swelling, tenderness of the limb, and limited range of motion which are seen in both conditions.[1] Imaging plays a very important role in the diagnosis, but is not always definitive and the preferred method of imaging in multifocal infections is not clear-cut. Current guidelines recommend MRI for diagnosis of acute osteomyelitis, though other imaging studies are often utilized. We will discuss the role of imaging in diagnosing osteomyelitis and provide a comprehensive literature review. A literature review was conducted via an electronic search of peer reviewed manuscripts regarding imaging studies in the diagnosis of osteomyelitis.

Osteomyelitis can be uni- or multifocal, when multiple sites of infection in the bones are affected. One study by Akakpo-Numado et al. described the specific sites common to children with sickle cell disease and osteomyelitis. Of the 43 children in this study, 11 had multifocal osteomyelitis and 32 had unifocal.[2] This study found that the most common sites were the long bones, including humeral (18 cases), tibial (12 cases), femoral (9 cases), fibular (7 cases), radial (7 cases), and ulnar (4 cases). The 6 short bones included 3 metacarpals and 3 phalanxes.[2] Though uncommon, children with sickle cell disease are more prone to multifocal osteomyelitis, in which disease course and complications are typically much worse. For example, as described by Caberet et al., a 2-year-old boy with multifocal osteomyelitis presented in sepsis and had complications throughout the course, including cardiopulmonary arrest and severe neurological damage.[3] Table 1 summarizes the multifocal osteomyelitis cases in children found in the literature, from years 2010–2019.

Regarding imaging, plain radiographs are recommended as the initial study of choice. Typical findings are elevation of the periosteum, a well-circumscribed lucency denoting an abscess and soft tissue swelling.[4] These findings are not unique to osteomyelitis, as they can denote other infectious processes or even a vaso-occlusion in an adjacent cortical bone. Although these findings are not unique to osteomyelitis, x-rays are useful as they can rule out fractures and are helpful for comparison with follow-up radiographs.[4] It is important to note that plain radiographs are usually normal for the first 10 days after symptom onset.[5]

An option for early imaging is bone scintigraphy (bone scan) because these images can detect changes within the first 2–3 days of infection.[5] Bone scans are performed using disphosphonates to detect osteoblastic activity. There will be increased uptake of the radionuclide tracer in areas with increased bone turnover, as in osteomyelitis. Images are taken in three sequences: angiogram, blood pool, and delayed bone phase.[5] The bone scan will show an increasing amount of uptake of the radionuclide.[6] There may also be increased uptake in the surrounding bone and tissue.[7] The bone scan is also useful in evaluating multifocal osteomyelitis and determining osteomyelitis versus cellulitis, because whole body images can be obtained.[6] This scan is highly sensitive, with a 90% sensitivity rate for detecting osteomyelitis.[5] One limitation to bone scans is that the specificity is low (35%).[5] If the bone has been violated, such as in a trauma or surgery, the specificity may be lower.[4] The high osteoblastic activity that is detected can be a result of causes other than osteomyelitis, such as the resolution of cortical bone damage from a

TABLE 1 Summary of multifocal cases cited in the literature review from years 2010–2019.

	Case	Bacterial culture	MRI reading	Bones involved	Other sequela seen on Imaging
1	Caberet, et al.[4]	Salmonella non typhi	Definitive on Bone scan, sequela seen on ultrasound	L humerus, left ulna, R radius, and R femur	Subperiosteal abscess and osteolysis, bone sequestration
2	Kao, et al.[16]	No growth	Probable	Humerus, radius, ulna	Abscess, muscle edema, effusion, osteonecrosis
3	Kao, et al.[16]	Salmonella enterica	Definitive	Humerus, tibia	Abscess, muscle edema, effusion
4	Kao, et al.[16]	Salmonella species	Probable	B/L first metatarsals	Abscess, osteonecrosis
5	Kao, et al.[16]	No growth	Probable	Distal femur, proximal tibia, tarsals, metatarsals	Abscess, effusion
6	Kao, et al.[16]	Salmonella species	Probable	Superior pubic ramus, femur	Muscle edema, effusion
7	Kao, et al.[16]	No growth	Probable	Humerus, radius, ulna	Abscess, muscle edema, effusion, osteonecrosis
8	Kao, et al.[16]	No growth	Suspected	B/L Ilia	Muscle edema, osteonecrosis
9	Kao, et al.[16]	No growth	Suspected	B/L Acetebula, femur	Muscle edema, osteonecrosis
10	Kao, et al.[16]	Salmonella species	Probable	Humerus, radius, ulna	Muscle edema, effusion
11	Kao, et al.[16]	No growth	Probable	B/L Parietal Bones	Abscess, effusion, osteonecrosis

vaso-occlusive crisis. These scans can further be hard to interpret with vertebral osteomyelitis, given the vascular structures overlying the vertebrae.[4] This imaging modality is typically used if MRI is contraindicated.

MRI is preferred for determining the diagnosis of osteomyelitis due to its sensitivity, specificity, and ability to depict great anatomic detail.[4] MRI does not use radiation but is just as sensitive, and more specific than bone scintigraphy.[8] On MRI we also see complications such as abscesses and sinus tracts, making it more valuable than bone scintigraphy in such cases.[8,9] T1-weighted images are used to evaluate the anatomy with precision and detail. On these images, "fluid will be dark, or have low signal, abscess will have a low to intermediate signal, and fat will have a high signal".[4] T2-weighted images are fluid-sensitive, meaning fluid will have a high signal and will be bright on imaging. Contrasted MRI is the study of choice for characterizing abscesses and epiphyseal infections.[4]

The most acute finding of osteomyelitis on MRI is bone marrow edema. Healthy marrow will have a high signal on T1 due to the amount of fat present; in osteomyelitis the marrow is filled with pus, leading to a low signal on imaging.[4] Abscesses and sinus tracts on T1 will be low signal, with a ring of intermediate signal delineating the abscess. If contrast is used, this rim will be enhanced because it is hypervascular granulation tissue. This is called the penumbra sign.[4] Another feature seen on MRI is periostitis, which will be depicted by low-signaling periosteum that is listed off the cortical surface. Extramedullary fat globules will be high-signaling.[4]

The limitations to using MRI is that findings will persist after resolution of the osteomyelitis. It is always important to correlate imaging findings with the clinical pictures.[4] The specificity is less than the sensitivity necessary for osteomyelitis, as the findings can also resemble other diagnoses, such as osteoid osteoma, stress injuries, reactive osteitis, malignancy, and neuropathic arthropathy.[4] In patients with sickle cell disease, it can be difficult to interpret MRI readings or decipher between osteonecrosis and osteomyelitis. The chronic changes of sickle cell disease will appear as linear hypointense changes in metaphysis and epiphysis.[9] MRI is not feasible for patients with permanent pacemakers and involves additional risks in young children who need sedation. Furthermore, it is costly, and not always accessible.[4]

In addition to the difficulties of diagnosing osteomyelitis already discussed, diagnosing multifocal osteomyelitis can bring further difficulties. An MRI shows one specific body part, but if multiple locations in the body are suspected to be affected, multiple MRIs are needed to properly evaluate all locations. Whole-body MRIs have been performed, but there is no standardization of protocols and findings from adult population imaging are hard to relate to the pediatric population. One

literature review on the use of whole-body MRIs found that 15 papers were devoted to the use of whole-body MRI in chronic non-bacterial osteomyelitis. It was found that "the body area covered, the sequences used, and the technical details vary significantly" from institution to institution. However, only a small number of studies address the validity of whole-body MRI.[10] There is a lack of standardized interpretation of these results, which can result in an error in diagnosis and treatment.[10] Literature is also lacking on the use of whole-body MRI in patients with multifocal infections. Another study looked at the practice of whole-body MRI by sending surveys to members of the Society for Pediatric Radiology. 49% of radiologists surveyed agreed that whole-body MRI is the preferred imaging modality for disseminated/multifocal infections.[11] This survey also denoted "some variability in exam utilization and technical performance practices among those pediatric radiologists who perform whole-body MRI".[11]

This is where PET-CT scans can be utilized. Literature about the utility of PET-CT for imaging multifocal bacterial osteomyelitis or other multifocal infections is not extensive. PET scans are a type of nuclear medicine scan that uses Fluorine-18 fluorodeoxyglucose, a positron-emitting radiopharmaceutical that localizes to hypermetabolic tissues that have high glucose uptake.[4] PET scans have the highest sensitivity and specificity. The advantages of PET scans include a quick turnaround time of 1.5–2 h, optimal spatial resolution, high target-to-background contrast, accurate anatomical localization of sites of abnormality, whole-body coverage, lack of artifacts due to metallic hardware, and absence of reactions due to administered pharmaceuticals.[12] In contrast to bone scintigraphy, FDG uptake will normalize in 2–3 months, whereas it takes much longer to normalize bone scans making them less reliable. This means that there will be less false-positive results for osteomyelitis when using PET scans in the setting of recent fractures.[12] One study looked at the utility of PET scans in infectious disease processes. In this study, an infectious disease physician evaluated each patient case with and without the PET results and considered the PET useful if it altered the diagnosis. Of the 56 cases, PET was considered positive in 31 of the cases. Of these 31 cases, 29 were treated for osteomyelitis.[13] The sensitivity was 90% and the specificity was 85% and the study determined that PET results affected clinical management in 67% of cases.[13] This study ultimately concluded that PET "is not warranted, as the outcome is frequently no change in management".[13] However, the PET scan was correct nearly in every case of osteomyelitis. Limitations of PET-CT include cost and a lack of availability in some hospitals.[4]

A recent study conducted at Children's National relied on MRI readings to categorize their patients.[2] Interestingly, out of the 28 patients treated for osteomyelitis, 18 (36%) had MRI readings considered consistent with osteomyelitis. The other 10 (39%) had readings indeterminate for osteomyelitis.[2] This means a large proportion of the patients did not have a definitive diagnosis after imaging. The findings from this study are important in demonstrating that even with imaging, osteomyelitis cannot be definitively diagnosed. In a study by Umans, 100% of osteomyelitis versus vaso-occlusive crisis cases were identified correctly based on enhancing MRI patterns.[14] Based on this study's MRI reads, an acute infarct demonstrated thin, linear rim enhancement on MRI while osteomyelitis revealed more geographic and irregular marrow enhancement. Two of four cases of osteomyelitis also demonstrated subtle cortical defects with abnormal signal traversing marrow and soft tissue.[14] In one study by Berger, et al., 31 cases were studied for osteomyelitis. Of the 31, 29 had MRI readings consistent for osteomyelitis. Only 9 of these 29 patients had positive blood cultures confirming the diagnosis.[1] There was an additional case that had a positive blood culture, but the MRI reading was equivocal. Many of the patients had multiple imaging modalities performed. "Nine cases were confirmed on magnetic resonance imaging, 13 on radiography, 8 on ultrasound, 1 on technetium bone scan, and 7 on gallium scan".[1]

Another large tertiary center queried their database to determine the diagnostic probability of imaging and microbiology for osteomyelitis. Out of 20 cases of osteomyelitis, imaging was obtained in 19.[15] Of these cases, four (21%) of them had imaging considered definitive for osteomyelitis.[15] Ten cases (53%) had imaging that was considered probable, and 5 cases (21%) were suspected osteomyelitis.[15] Of the nine cases that also had culture proven osteomyelitis, MRI findings were definitive in only two cases (22%), probable in four (44%), and suspected in three cases (33%).[15] This case highlights the limitations of using strictly MRI for diagnosis.[15] Table 2 summarizes MRI and PET findings.

As evidenced by our case and the overview of the literature, it is extremely difficult to differentiate between an acute vaso-occlusive crisis and osteomyelitis in a patient with sickle cell disease. It is even more difficult to diagnose multifocal osteomyelitis. Physicians should keep in mind that as some studies suggest, a pain crisis is 50 times more common than osteomyelitis in a patient with sickle cell disease.[1] There is currently no gold standard diagnostic work-up. The pros and cons of imaging modalities are summarized in Table 3. Great care must be taken in these cases, as an erroneous diagnosis can lead to unnecessary antibiotics, future antibiotic resistance, PICC line placements, and complications that come with this, including deep venous thromboses.[1] However, missing osteomyelitis can be detrimental—causing chronic osteomyelitis and bone deformities.[1] Each case must be evaluated

TABLE 2 Describes the cases from the literature review and their MRI and PET readings.

Case	Imaging	Definitive?	Other comments	Conclusion
Cases 1–18 from Weisman, et al.	MRI	Considered consistent with osteomyelitis.	All patient treated, cultures positive in 9 of the 28 patients, negative in the rest.	"OM continues to pose diagnostic challenges. Most patients are treated for OM without definitive confirmation"
Cases 19–28 from Weisman, et al.	MRI	Considered indeterminate in diagnosing osteomyelitis	All patient treated, cultures positive in 9 of the 28 patients, negative in the rest	"OM continues to pose diagnostic challenges. Most patients are treated for OM without definitive confirmation"
Case 1 from Umans, et al.	MRI	Considered definitive for osteomyelitis	"Demonstrated elongated, serpiginous central medullary enhancement with periostitis"	"MRI may allow accurate distinction between acute infarct and osteomyelitis"
Cases 1–29 from Berger, et al.	MRI	Considered definitive for osteomyelitis	9 had positive blood cultures, 20 had negative cultures	"By identifying whether a patient has risk factors, physicians can make a more informed choice in deciding whether to proceed with radiological investigations and bone aspirate for culture and when to initiate a prolonged course of antibiotics as treatment for osteomyelitis"
Cases 30 from Berger, et al.	MRI	Considered definitive for osteomyelitis	This patient had a positive blood culture	"By identifying whether a patient has risk factors, physicians can make a more informed choice in deciding whether to proceed with radiological investigations and bone aspirate for culture and when to initiate a prolonged course of antibiotics as treatment for osteomyelitis"
Cases 1–4 from Kao, et al.	MRI	Considered definitive for osteomyelitis	There was no growth on 3 of the cases blood cultures, these were also noted to be unifocal. However, two of these had operative culture growth. One of the cases was multifocal and did have a positive blood and operative cultures	"Highlights the limitations of MRI as the only diagnostic tool for identifying OM"
Cases 5–15 from Kao, et al.	MRI	Considered probable for osteomyelitis		"Highlights the limitations of MRI as the only diagnostic tool for identifying OM"
Cases 16–18 from Kao, et al.	MRI	Suspected for osteomyelitis	Of these cases, one had a positive blood culture and was unifocal. The other two showed no growth on blood culture, and were also considered multifocal	"Highlights the limitations of MRI as the only diagnostic tool for identifying OM"
Cases 1–31 from Uy, et al.	PET	Considered positive for osteomyelitis	Only 29 of the 31 were diagnosed with osteomyelitis	"If OM is already strongly suspected or ruled not clinically likely, imaging with PET scan is not warranted, as the outcome is frequently no change in management"

TABLE 3 Summarizes the imaging modalities used to diagnose osteomyelitis, as well as their pros and cons.

Imaging modality	Pros	Cons
Plain radiograph	• Can rule out other causes such as fractures. • Can use for comparison later • Can see abscesses, elevation of the periosteum, and soft-tissue swelling	• Findings are often non-specific to osteomyelitis. • Still uses radiation
Bone scan	• Can detest changes within 203 days • Useful in differentiating osteomyelitis vs. cellulitis. • Useful in multifocal disease in particular, because easy to scan whole body. • High sensitivity • Can use if MRI is contraindicated	• Low specificity, especially if there was previous trauma or surgery to the bone. • Limited in evaluation of suspected vertebral osteomyelitis due to high vascularity. • FDG uptake takes a prolonged time to normalize, which means more false positives in the setting of recent fractures.
MRI	• High sensitivity and specificity • Lack of radiation • Can see complications of osteomyelitis, including abscesses, sinus tracts, and periostitis.	• Findings persist even with the resolution of the osteomyelitis. • Findings can resemble other diagnoses, such as osteonecrosis, osteoid osteoma, reactive osteitis, malignancy, and neuropathic arthopathy. • Amount of radiation • Can be expensive • Lack of availability • May need sedation in young children • Cannot use if patient has any metallic hardware • Would need multiple images if multifocal disease is suspected. Not much in literature regarding whole-body MRIs in children.
PET	• High sensitivity and specificity • Quick turnaround time • Can easily get whole-body coverage • Lack of artifacts due to metallic hardware • Absence of reaction to administered pharmaceuticals • FDG uptake normalizes in 2–3 months, which means less false positives.	• Expensive • Lack of availability

individually with focus on the history, the physical exam, the laboratory work-up, and imaging findings. In patients with sickle cell disease, we must be more cognizant of the possibility of multifocal osteomyelitis. While MRIs will be accurate in these cases, PET scans can be more efficient in whole body imaging and have greater sensitivity and specificity in diagnosing osteomyelitis.

AUTHOR CONTRIBUTIONS

Megan Scruggs: Investigation; methodology; project administration; resources; writing – original draft; writing – review and editing. **Irina Pateva:** Conceptualization; investigation; project administration; resources; supervision; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

None of the named authors has a conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

CONSENT

The patient's parent was appreciative of the care the patient received. Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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