

Candida parapsilosis-Caused Arthritis with Rice Body Formation: A Case Presentation and Literature Review

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Abstract: A 68-year-old male patient came to the orthopedics department because of swelling and pain in his left shoulder joint. He received more than 15 intraarticular steroid injections in the shoulder joint at a local private hospital. MRI showed that the synovial membrane of the joint capsule was thickened and swollen, and there were extensive “rice body-like” low T2 signal shadows filling. Arthroscopic removal of rice bodies and subtotal bursectomy were performed. The observation channel was placed through the posterior approach, and a large amount of rice bodies in yellow bursa fluid were observed to flow out. Rice bodies with a diameter of approximately 1–5 mm filled the joint cavity were seen in the observation channel. The histopathological examination of the rice body showed that it was mainly composed of fibrin without a clear tissue structure. Bacterial and fungal cultures of synovial fluid suggested *Candida parapsilosis* infection, so the patient received antifungal treatment. However, the shoulder swelled again after three weeks, MRI revealed that there was significant fluid accumulation in the subacromial-subdeltoid region with necrotic synovial tissue floating and ultrasound examination showed joint cavity effusion, synovial hyperplasia, and some synovium looked like “floating weeds”. After 2 weeks, there were recurrent rice bodies in the articular cavity. Arthroscopic surgery was performed again to clean the joint and a catheter was placed for irrigation and drainage, and a large amount of necrotic synovial tissue floating as seen in ultrasound. Finally, patient received sensitive antifungal treatment and did not relapse within 6 months. During the recurrence in the current case, we recorded the process of rice body formation, which has for the first time been reported.

Keywords: rice body formation, *Candida parapsilosis*, fungal arthritis, intraarticular injection, corticosteroids

Introduction

As a rare disease, rice body is considered a non-specific response to chronic inflammation and was first described as being associated with tuberculous arthritis.¹ Current research suggests that rice body is most common in rheumatoid arthritis,^{2,3} but there are also a few reports suggesting that rice body formation is related to trauma,⁴ juvenile idiopathic arthritis,⁵ seronegative inflammatory arthritis,⁶ infection,^{7,8} graft reaction,⁹ and even osteoarthritis.¹⁰ Almost all rice bodies are formed in the joint bursa or tendon sheath, but there are also reports suggesting the formation of rice bodies may occur without any joint connection.²

Candida parapsilosis infections of the intraarticular region are also extremely rare, though they may occur in patients treated with systemic immunosuppressants or after joint replacement.¹¹ The diagnosis of fungal arthritis strictly relies on fungal culture, and there is a certain rate of missed diagnosis, which leads to delayed treatment.¹² In this article, we report a rare case of articular infection of *Candida parapsilosis* with the formation of a rice body after repeated intraarticular injections.

Case Report

A 68 years old male patient came to the orthopedics department because of pain and swelling of the left shoulder joint. The patient developed left shoulder joint pain without obvious incentive 6 months prior, and there was no obvious shoulder joint swelling or limited shoulder joint movement at that time. He received more than 15 irregular intraarticular steroid injections in the shoulder joint at a local private hospital. The pain was significantly relieved within 1 week after each injection, but it recurred. One month prior to presentation, the patient had aggravated pain in the left shoulder joint, and the joint gradually swelled with obvious limitations of abduction and internal rotation. He had a history of fracture in his left shoulder 20 years earlier. Due to the age of the injury, the details could not be traced. No surgical treatment was performed at that time, and he recovered well. Physical examination found local swelling and tenderness in the shoulder, with limited range of motion. The patient had no fever, rheumatic disease, tuberculosis, or immunosuppressive drugs. The blood test indicated a white blood cell count of $5.43 \times 10^9/L$, a C-reactive protein (CRP) level of 3.27 mg/L, an erythrocyte sedimentation rate of 17 mm/h, a rheumatoid factor less than 20 IU/mL, and positive results from T-spot and TB-Ab tests.

Plain radiography (Figure 1A and B) and CT scan (Figure 1D–F) showed bone erosion at the humeral head, the subchondral portion of the glenoid and the acromion. MRI (1.5) showed uneven signal increases in the humeral head, acromion and glenoid, articular cartilage wear, massive tears of the supraspinatus, subacromial space communication with the glenohumeral joint, and subdeltoid bursa communication with the glenohumeral joint cavity. The synovium of the joint



Figure 1 Imaging of *Candida* septic arthritis in the left shoulder. (A and B): Anteroposterior (A) and Supraspinatus export (B) radiographs of the left shoulder show bone erosions at the acromion, glenoid and humeral head. (C): T1-weighted image showing no obvious “rice body”-like structures in the enlarged bursa. (D–F): CT scans showed clearer bone destruction at the acromion, glenoid and humeral head. (G–I): T2-weighted image shows hundreds of rice bodies in the subacromial-subdeltoid bursa, subcoracoid bursa and a large rotator cuff tear. (J–L): MRI T1 after gadolinium enhancement shows that the synovial membrane was obviously enhanced, but the rice body formations were not.

was thickened and swollen, and there were extensive “rice body-like” low T2 signal shadows filling (Figure 1G–I). The enhanced gadopentetate with meglumine scan showed obvious enhancement of the synovium in the T1 sequence, but no enhancement was found in the rice body formation inside the bursa (Figure 1J–L).

Considering that infectious diseases needed to be ruled out and discussions about surgical procedures such as rotator cuff repair and shoulder joint replacement would have to wait, arthroscopic removal of rice bodies and subtotal bursectomy were performed. The observation channel was placed through the posterior approach, and a lot of rice bodies in yellow bursa fluid were observed to flow out (Figure 2A and B). After the lens was placed, rice bodies with a diameter of approximately 1–5 mm filled the joint cavity (Figure 2C and D). Placing the shaver through the lateral approach, the field of vision became clear after removing most of the rice bodies. We found a spontaneous rupture of the long head tendon of the biceps brachii and a large rupture in the supraspinatus; the subacromial space was connected to the joint through this rupture. Three arthroscopic approaches (posterior approach, anterior approach and lateral approach) were used to monitor and operate and to fully explore the subacromial bursal, subdeltoid bursal, the periglenoid and the anterior spaces of the subscapularis. The rice body and denatured synovial tissue were fully shaved. Postoperative MRI showed that although the swelling around the joint was obvious, there was no remaining rice body (Figure 2G and H).

The histopathological examination of the rice body showed that it was mainly composed of fibrin without a clear tissue structure, with some small amount of tissue and cell coagulation (Figure 2E and F). A PCR test for the detection of *Mycobacterium tuberculosis* DNA suggested negative results, and bacterial and fungal cultures of synovial fluid suggested *Candida parapsilosis* infection performed by Vitek-2 (BioMerieux, France) automated system. However, peripheral blood culture showed no bacterial or fungal proliferation. Drug sensitivity test (DST) indicated that voriconazole, itraconazole, fluconazole, 5-flucytosine, and amphotericin are susceptible. Therefore, the patient received fluconazole (400 mg/qd) intravenously for 1 week, and then oral administration (200 mg/bid) to sequential therapy for 8 weeks as planned.

However, the shoulder swelled again after two weeks of oral administration (Figure 3E). MRI revealed a lot of fluid accumulation in the subacromial-subdeltoid region with necrotic synovial tissue floating (Figure 3A and B). In view of the large amount of fluid accumulation in the joint cavity, the joint cavity puncture was performed, and about 100 mL of yellow turbid liquid was extracted. The fungus culture showed that there was still *Candida parapsilosis*. Then the joint cavity was punctured for many times due to repeated swelling of the shoulder joint. Ultrasound examination showed joint

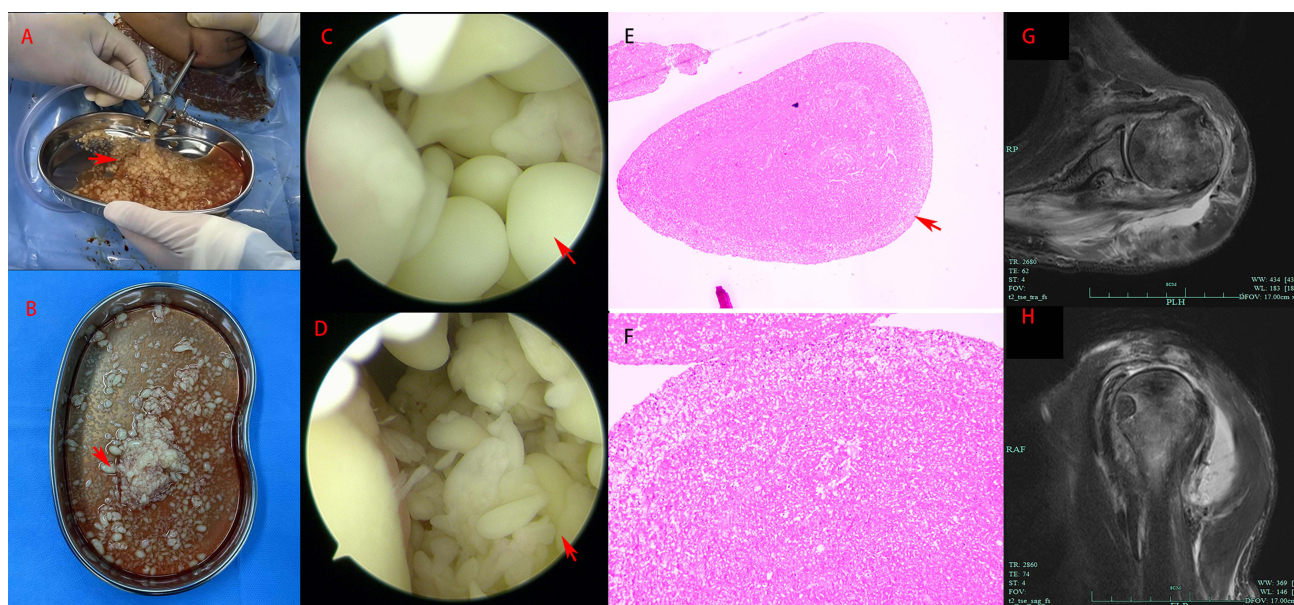


Figure 2 Macroscopic view and histopathology of rice body formation and postoperative images. (A): Rice bodies and yellow bursa fluid were removed after the channel was placed. (B): Yellow bursa fluid and rice bodies of various sizes (approximately a few millimeters). (C and D): Arthroscopic observation of rice bodies of different sizes and smooth surfaces. (E and F): Histopathology suggests that the rice body is mainly composed of fibrin material with inflammatory cells. (G and H): Postoperative MRI showed complete removal of rice bodies.

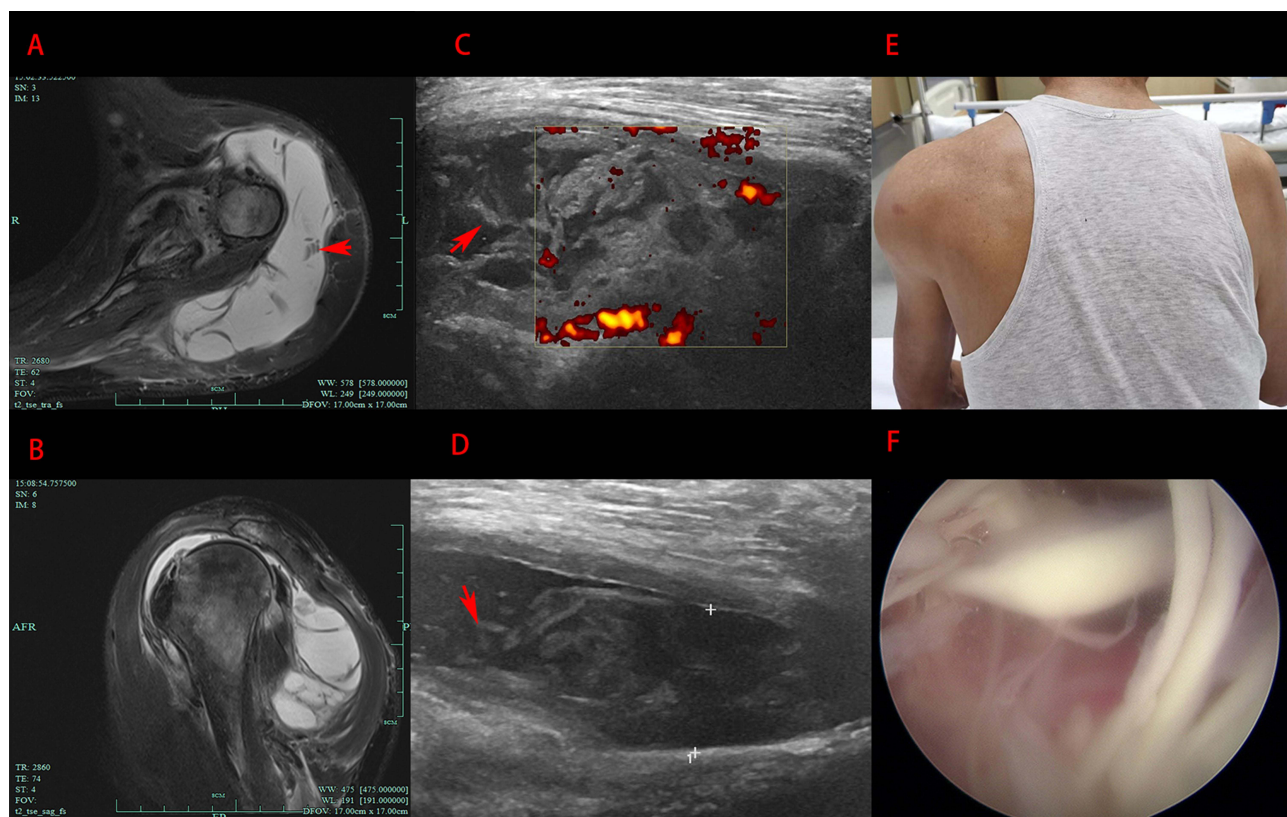


Figure 3 Disease record during recurrence. (A and B): T2-weighted image shows a lot of fluid accumulation in the subacromial-subdeltoid region with necrotic synovial tissue floating. (C and D): Ultrasound examination showed some synovium looked like ‘floating weeds’. (E) Apparent joint swelling of the patient. (F): The necrotic synovium floating in the joint cavity and not completely detached under arthroscopy.

cavity effusion, synovial hyperplasia, and some synovium looked like “floating weeds” (Figure 3C and D). In view of the recurring symptoms, arthroscopic surgery was performed again to clean the joint and a catheter was placed for irrigation and drainage (1 for irrigation and 1 for drainage). Under arthroscopy, there is no obvious rice body formation in the joint cavity, but a large amount of necrotic synovial tissue floating as seen in ultrasound (Figure 3F). A large amount of necrotic tissue flows out from the drainage tube and was pulled out due to blockage 10 days later. After operation, 400mg voriconazole was given intravenously, and 200mg bid was taken orally after three consecutive negative cultures. At present, the patient has received oral treatment for 8 weeks and change to the fluconazole (200 mg/bid) 4 weeks for the damage of liver function, without swelling again, and the subsequent culture is negative. The patient has been treated for 6 months and has not recurred.

Discussion and Review of the Literature

Rice body formations were described in tuberculosis joints by Riese in 1895 in the first time¹ and have been observed in various chronic nonspecific inflammations of joints/bursae/tendon sheaths, such as systemic immune abnormalities, infection and degeneration. In our comprehensive literature review (Table 1), We found that rice bodies are most commonly seen in rheumatoid arthritis,^{2,3,13–15} it can occur in systemic juvenile rheumatoid arthritis,^{5,16} seronegative rheumatoid arthritis,⁶ injury,⁴ graft reaction,⁹ bacteria/fungi/mycobacterium tuberculosis infections,^{1,7,8,17,18} Milwaukee shoulder, radiotherapy damage,¹⁹ camptodactyly, osteoarthritis,¹⁰ and even in conditions of unknown etiology.^{20–23} Rice body formation in *Candida parapsilosis*-induced arthritis is very rare and has been reported only once.⁸ Fungal infections in the joints are extremely rare, and common risk factors may be systemic immunosuppression, such as immunosuppressive therapy or postoperative joint prosthesis.¹¹ The report made by Jeong et al⁸ showed a case of *Candida parapsilosis* infection in an immunocompetent patient whose risk factors were old age and unexplained operation before 18 months. In this case, the patient had several corticosteroid injections into his shoulder, which might have caused the

Table 1 Clinical Characteristics of Patients with Rice Body Formation.

Years	Author	Number of Cases	Age/Sex	Location	Symptom	Pathogeny	Pathology	Treatment	Complication	Follow-Up Time
1996	J. F. GRIFFITH ²⁵	2	54/F	Subacromial/ Subdeltoid	P/S	None	Fibrinous material	Synovectomy	None	3M
			51/F	Subacromial/ Subdeltoid	P/S	Rheumatoid arthritis	None	None	None	None
1998	L.D. Spence ²⁶	1	25/F	Bicipitoradial bursa	P/S	None	Fibrinous material	Surgery	None	None
1998	D.E.Muirhead ⁴	1	9/M	Medial malleolus (extra-articular)	S	Thorn injury	Diffuse cellular component, collagen septa, electron dense fibrillary	Surgery	None	24M
2000	I. Sugano ²⁷	4	28/F	Shoulder	S	None	Massive fibrin fibrils and a few collagen fibers produced by fibroblastic cells	Bursectomy	None	None
			50/F	Shoulder	P/S	None	Fibrin fibrils and collagen fibers	Bursectomy	None	None
			44/M	Shoulder	P/S	None	Fibrin fibrils and collagen fibers	Bursectomy	None	None
			82/M	Flexor synovial sheath	S	None	Fibrin fibrils and collagen fibers	Surgery	None	None
2002	A. Chen ²¹	1	42/M	Subacromial/ Subdeltoid	S	None	Fibrinous material	Surgery	None	None
2002	R. Kim ¹⁸	1	41/F	Subdeltoid	P/S	Mycobacterium tuberculosis	Eosinophilic material inner core surrounded by collagen and fibrin	Arthroscopic debridement and biopsy and anti-tuberculous chemotherapy	None	18M

(Continued)

Table I (Continued).

Years	Author	Number of Cases	Age/Sex	Location	Symptom	Pathogeny	Pathology	Treatment	Complication	Follow-Up Time
2002	J Li-Yu ¹⁰	8	75/M	Shoulder	P/S	Milwaukee shoulder	The rice bodies were composed of uneven strands of fibrin with typical striations. Some areas exhibited collagen fibers embedded in amorphous material. There were, likewise, occasional viable appearing or degenerated cells scattered within the fibrin. Cells were mononuclear, mostly macrophages, and occurred on the surface or within the fibrinous network.	None	OA, rotator cuff tear Bone erosions	None
			63/M	Proximal interphalangeal point	S	None				
			62/F	Knee	P/S	Rheumatoid arthritis and Osteoarthritis				
			5/M	Knee	P/S	Camptodactyly				
			50/M	Knee	P/S	Osteoarthritis				
			64/M	Shoulder	P/S	None				
			75/M	Subacromial bursa and shoulder joint	S	Staph aureus septic bursitis and arthritis				
			46/F	Knee	P/S	Osteoarthritis				
2004	H. Mutlu ²⁸	1	4/F	Subacromial-subdeltoid bursa and knee joint	S	None	Osteochondral bodies encased by fibrinous material	Rice bodies without synovium removed	None	12M
2004	T. Matsumoto ²⁹	1	73/F	Olecranon	S	None	Fibrinous material	Bursectomy	None	20M
2006	C. Huang ³⁰	1	73/F	Trochanteric Bursitis	S	None	Eosinophilic fibrin core surrounded by reticulated and laminated fibrin	Bursectomy Surgery	NONE	9M
2006	A. Cuomo ¹⁶	1	4/M	Proximal long biceps tendon and extending distally into the plane between the biceps and brachialis	S	Systemic juvenile rheumatoid arthritis	Hyalinized outer surface and inner layers with embedded synovial cells and lymphocytes	Open excisional biopsy	None	6M

2007	M. Matzer ²	I	46/F	Shoulder and neck (not communicating with articulation t)	S	Rheumatoid arthritis	Fibrinous material	Surgery	None	None
2008	T. Ergun ²²	I	32/M	Flexor tendons of the wrist	S	None	Fibrin	Surgery	None	24M
2009	H. Nagasawa ³¹	I	68/M	Right distal forearm	P/S	None	Fibrinous loose bodies	Surgery	Spontaneous rupture of the flexor tendons	60M
2011	K. lyengar ⁶	I	72/F	Both of wrists	P/S	Sero-negative rheumatoid arthritis	Fibrinonecrotic material.	Subtotal synovectomy and Methotrexate	Recurrent swellings and paraesthesia.	12M
2012	R. Subramaniam ³	I	49/F	Shoulder	P/S	Rheumatoid arthritis	A central core of collagen fibers surrounded by fibrin on the periphery	Arthroscopic bursectomy and oral methotrexate and prednisolone	None	30M
2012	Forse, C. L ²³	I	51/M	Flexor tendons of the wrist	P/S	None	Fibrinoid proteinaceous material enveloped by neutrophilic debris	An open incisional biopsy	Symptoms of median neuropathy	12M
2013	Y. Jeong ⁸	I	74/M	Shoulder	P/S	Candida infection	Fibrin with some chronic inflammatory cells, hemorrhagic infarct, and dystrophic calcification	Drainage, bursectomy, and debridement and intravenous treatment with fluconazole	Full-thickness tear of the supraspinatus tendon and bone erosions	None
2014	S. Moreno ¹⁵	I	62/F	Finger tendon	S	Seropositive rheumatoid arthritis	Inner core of amorphous acidophilic material surrounding with thin fibrin layer	Surgery	Skin ulceration	6M

(Continued)

Table 1 (Continued).

Years	Author	Number of Cases	Age/Sex	Location	Symptom	Pathogeny	Pathology	Treatment	Complication	Follow-Up Time
2015	C Best ¹³	1	52/F	Subacromial-Subdeltoid Bursal	P/S	Rheumatoid arthritis	Noe	Surgery and oral sulfasalazine and methotrexate	Passive abduction and impingement maneuvers	None
2015	T.H. Lui ³²	1	58/F	Tendons in ankle	P/F	None	Fibrin material	Tendoscopic synovectomy	Dorsalis pedis psuedoaneurysm	23M
2016	S. Bayram ¹⁷	1	50/M	Flexor tendons in the wrist:	P/S	Sero-negative rheumatoid arthritis and M. tuberculosis	Granulomatous synovitis	Synovitis resection and flexor retinaculum release and antituberculosis therapy	None	12M
2018	F. M. Reda ³³	1	69/M	Thenar eminence	P/S	None	Chronic non-specific synovitis	Rice bodies were removed, and a thorough excision of the sheath	Compression of the median nerve	12M
2018	M. Cegarra-Escolano ²⁰	1	31/M	Volar side of the fourth finger	S	None	Synovial villi with rice bodies and central necrosis, and epithelioid granulomas	Surgery	None	12M
2018	Joshi. PS ¹⁴	1	54/F	Subacromial/subdeltoid bursa	P/S	Rheumatoid arthritis	Fibrin deposition with fibroblast and mononuclear cells	Arthroscopic loose body excision and sub-acromial bursectomy and anti-rheumatic drugs	None	12M
2019	S. J. Barad ⁹	1	48/M	Subacromial-subdeltoid	P/S	Regeneten bioinductive implant	None	Washout, debridement, and placement of tubes for drainage.	None	3M

2020	J. Guo ¹⁹	2	27/F	Subacromial/ subdeltoid bursa	S	Rheumatoid arthritis	Fibrous tissue wrapping necrosis with chronic inflammatory cells	Arthroscopic surgery	None	24M
2021	P. Bhat ⁷	1	45/F	Subacromial/ subdeltoid bursa	S	Radiotherapy to breast cancer	None	Breast cancer	None	24M
			68/F	Hip	P/S	Intramedullary (IM) rod placement and infection of Haemophilus parainfluenza	Acellular fibrinous debris and granulation admixed with neutrophilic inflammatory cells	Complete evacuation of the large complex cyst and amoxicillin- clavulanate	None	None
2022	S. Vyas ³⁴	1	29/F	Shoulder	S	Rheumatoid arthritis	None	Local steroids	None	6M
2022	Z Haibo ³⁵	1	50/F	Knee	P/S	None	None	Arthroscopic surgery	None	None
Summary	30 reports	42 patients	4–82 years old Female >male	Widely distributed, mostly in tendon sheath and shoulder bursa	Swelling, possibly accompanied by pain	Rheumatoid arthritis and various infections, but often unknown	Fibrin material with Inflammatory cells infiltration	Surgery with treatment of primary disease	Few complications according to the site and the primary disease,	Good follow-up prognosis

impairment of immunity. What is more, injectable corticosteroids contaminated with fungal strains will greatly increase the chances of infection. The New England Journal of Medicine disclosed the fungal infections associated with coordinated methylprednisolone injections with substantial morbidity and mortality in 2013.²⁴ In addition, according to patient's description, the sterile procedures were not strictly implemented in the process of configuration and injection which make it easier for patients to be inoculated with pathogens.

The pathogenesis of rice body formation remains largely unknown and usually occurs secondary to nonspecific responses to synovial inflammation. Some researchers believe that the rice body is initially formed in synovial fluid and increases with fibrin aggregation.^{4,36} Other researchers believe that intra-articular synovitis, microinfarct after ischemia and necrosis, subsequent detachment of necrotic synovium into the articular cavity, and fibrin encapsulation in synovial fluid are the most likely reasons.^{18,37,38} In the recurrent process of this case, we found the process of synovial necrosis and shedding through MRI and ultrasound examination, which was not reported in the previous literatures, so we tended to be secondary pathogenesis process. After a literature review, we suggested that the above two mechanisms may exist at the same time or that there may be different mechanisms in different etiologies, because the performance of rice bodies is inconsistent in different reports. Some reports suggested that there are thousands of rice bodies,^{8,14,18} while some cases indicate fewer.^{3,39} Most of the rice bodies are small in diameter, while a few reports describe the rice bodies as being large in diameter.^{3,27} Most of the rice bodies were not visible on X-ray, while a few cases were revealed by X-ray.^{29,35} Moreover, the osteochondral erosion described in this article is relatively rare but was reported in a previous article that was also related to fungal infection.⁸ Almost all rice body formation is seen in a single joint, only Mutlu²⁸ reported a case of simultaneous involvement of the shoulder and knee joints. The above differences may be related to the course and the location of the disease, but we believe that the most likely relationship is the etiological factor. However, due to the low incidence and currently unreproducible animal experiments, the above inferences cannot be scientifically proven.

Histopathologically, rice bodies are mostly composed of irregular and inhomogeneous fibrin material with inflammatory cell infiltration, but some observers have reported a more regular fibrin outer membrane. The ultrastructure of rice bodies under electron microscope is rarely mentioned. Muirhead et al⁴ reported that the ultrastructure of the electron dense material was fibrillary and exhibited an axial periodicity at high magnification, consistent with that of fibrin in rice bodies. The ultrastructure of the outside membrane was shown to be a mixture of collagen infiltrating fibroblasts, inflammatory cells and macrophages. Li-Yu et al¹⁰ reported that the rice body consists of coarse fibrin and fine fibrin with typical stripes. The existence of typical tiny apatite like crystals was confirmed by electron microscope.

Bone erosion can be observed on plain radiographs and CT scans, and if mineralized, rice bodies may also be noted. Ultrasound and MRI are very important imaging techniques for diagnosing rice body bursitis/synovitis due to the nonspecific symptoms of swelling, not necessarily pain.^{25,26,30,40} Huang et al³⁰ suggested that sonography facilitates accurate preoperative diagnosis by explicit delineation of the dissection tract and the characteristic fried rice pattern of rice bodies. From the literature review, consistent with the current case, MRI was the most important examination in diagnosis of rice body. The MRI characteristics of the rice body have been clearly described. The low- and medium-signal nodules on T1-weighted images may not be clearly demarcated from the bursa fluid, and there is clear, relatively low signal filling on T2 images. The bursa was enhanced, while rice bodies were not after enhancement. Rice body formation needs to be distinguished from pigmented villonodular synovitis and synovial chondromatosis. The bodies of synovial chondromatosis contain cartilage components, so the T2 sequence shows a high signal, which can be distinguished from rice granules. Pigmented villonodular synovitis can be seen as diffuse hyperplasia of synovial villi, nodular changes and deposition of hemosiderin, usually showing a low signal in T1 and T2 sequences, and MRI different FE sequences can prove the presence of hemosiderin.⁴¹

In terms of treatment, surgical removal of rice bodies and diseased synovium is the current consensus, and almost all have achieved good results, except for a case of tendon rupture after surgery reported by Nagasawa.³¹ Depending on the surgical site, open surgery or arthroscopy can be selected, or a combination of the two.^{3,32,33,42} Rice bodies are a non-specific inflammatory response. In addition to symptomatic treatment of rice grains and synovium, the treatment of primary disease is also very important. Vyas et al³⁴ reported a case of significant degeneration of the body during the treatment of rheumatoid arthritis with local steroids without any surgery because of the influence of COVID-19. In the current case, the primary disease was thought to be *Candida parapsilosis* infection, which was confirmed by fungal

culture. Biofilm formation on the surface of medical devices or prostheses or in host tissues is the pathogenic factor and mechanism of most *Candida* infections. Compared to *Candida albicans*, the biofilm of *Candida parapsilosis* is thinner and less structured, consisting only of clumped budding spores, which may be due to its lower pathogenicity.⁴³ Worldwide, resistance to antibiotics, including antifungals, is facing serious challenges, so drug sensitivity testing has tremendous significance in selecting the right antifungal drug.⁴⁴ Voriconazole has good synovial fluid permeability and good bioavailability, and has less nephrotoxicity than amphotericin.^{45,46} In this case of recurrent *Candida* arthritis, lavage combined with voriconazole showed a good effect.

Conclusion

We report a rare case of arthritis with rice body formation caused by *Candida parapsilosis* infection in an immunocompetent patient and the synovium changes in the early stage of rice body formation were reported for the first time. MRI and fungal culture are important for diagnosing this rare disease. Debridement or lavage and antifungal therapy according to susceptibility testing are effective. It is worth mentioning that the contaminated corticosteroid and unstandardized practice of corticosteroid injection may cause serious complications.

Consent for Publication

Written informed consent was obtained from the patient for images and the details of this case. Details of the case have been approved by the IRB of the Hangzhou Hospital of Traditional Chinese Medicine affiliated to Zhejiang Chinese Medical University.

Disclosure

Weihui Qi and Yanyun Ren are co-first authors for this study. The authors report no conflicts of interest in this work.

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