

A challenging diagnosis of rare co-existent multiple myeloma and prostate adenocarcinoma: a systematic review of case reports

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Abstract

Objective: To review biochemical parameters, clinical characteristics, demographics, radiological and histopathological findings, treatment modalities and outcomes used to examine patients with coexisting multiple myeloma and prostate adenocarcinoma.

Method: The systematic review comprised search on PubMed, Google Scholar, Science Direct and the Directory of Open Access Journal databases for case reports published till June 1, 2022. The search was done in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines using appropriate key words. Case reports included were those dealing exclusively with human subjects, were published in the English language and had free, full-text, public access. Quality assessment was done using Joanna Briggs Institute's Critical Appraisal Checklist for Case Reports. Data was extracted and the case reports were evaluated for demographic, diagnostic and treatment parameters.

Results: Of the 515 studies initially identified, 5(0.97%) were analysed; all males with mean age 68.6±10.78 years. The most common symptom reported at presentation was low back pain 3(60%), Osteolytic lesions were seen in 4(80%) patients on imaging with elevated prostate surface antigen levels. Anaemia was found in 3(60%) patients and 2(40%) had thrombocytopenia.

Conclusion: Multiple myeloma and prostate adenocarcinoma can coexist although it is rare. Awareness regarding the possible coexistence of the two prominent cancer types may further help clinicians during their practice in considering multiple myeloma as a differential diagnosis when encountered with patients having osteolytic bony lesions along with elevated levels of prostate-specific antigen.

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Introduction

Multiple myeloma (MM) is a neoplastic plasma cell proliferation that results in abnormally high synthesis of monoclonal immunoglobulins (IGs) and, eventually, organ damage. Hypercalcaemia, kidney damage, anaemia and bone pain with lytic lesions are some of the clinical signs of MM^{1,2}. The exact aetiology of MM is unknown, but alterations and translocations in the promoter genes, especially chromosome 14, are commonly found³. NRAS (neuroblastoma RAS viral oncogene homolog), KRAS (Kirsten rat sarcoma virus) and BRAF (v-raf murine sarcoma viral oncogene homolog B1) are oncogenes that may participate in the proliferation of plasma cells⁴. Obesity, alcohol consumption, environmental causes, such as organic solvents, insecticides and agent orange, and radiation exposure may also contribute to the disease^{5,6}. MM is a relatively uncommon haematological malignancy, accounting for only 1.8% of all new cases of cancer diagnosed each year in the United States. MM is more common in men and occurs predominantly in the geriatric population. African American and black populations are affected twice as much as white populations^{7,8}.

The most frequently identified male cancer and the main cause of death in males is prostate cancer^{9,10}. The early stages of prostate cancer are typically symptomless and have a slower growth pattern. However, the illness only exhibits late signs, such as anaemia-related lethargy, bone pain, spinal metastases that cause paralysis, and renal failure brought on by bilateral ureteral blockage¹¹. Older age, positive family history, hypertension (HTN), inactivity, consistently high testosterone levels, exposure to agent orange, and ethnicity are all risk factors for

prostate cancer^{12,13}. It has also been linked with obesity¹⁴.

Bony metastases in prostate carcinoma are osteoblastic, mixed osteoblastic/osteolytic, and pure osteolytic lesions. About 80% lesions are osteoblastic, 15% are mixed and only 5% are osteolytic in nature¹⁵. In almost 90% patients, bony metastases are present in the late/advanced stage of prostate cancer, while 30% patients at the time of diagnosis have evidence of bone metastasis¹⁶. Although there is a chance of osteomyelitis, metastatic carcinoma, leukaemia, lymphoma and Langerhan's cell histiocytosis, the main differential diagnoses for diffuse osteolytic bone based on imaging are metastatic prostate cancer and MM.¹⁷ Apart from similarities found in imaging, the two diseases share other important similarities, such as age at presentation, being more common in men, and presenting symptoms of bone pain and back pain. However, the real challenge is how to distinguish the two entities conclusively, and find a timely, definitive diagnosis because their treatment approaches and strategies differ significantly. This can be achieved by adopting a methodical, step-wise approach to investigating the patients by using certain important blood tests and also incorporating histopathological analysis. The prominent features of MM are the presence of anaemia, thrombocytopenia and hypercalcaemia, but not in diffuse osteolytic metastases in metastatic prostate cancer. Furthermore, plasma cells of MM on bone marrow

prostate cancer¹⁹⁻²³. The current systematic review was planned to investigate the uncommon coexistence of MM and prostate cancer, and to evaluate a possible association between the two.

Materials and Methods

The systematic review was done after it was registered with the International Prospective Register of Systematic Reviews (PROSPERO) online registry (PROSPERO identifier: CRD42022334906) on May 23, 2022, and comprised search on PubMed, Google Scholar, Science Direct and the Directory of Open Access Journal databases for case reports published till June 1, 2022. The search was done in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.²⁴ The search was conducted without using any automated tool. Medical Subject Heading (MeSH) approach was used, and Boolean operators were applied to appropriate key words. Selection of case reports was done by two reviewers independently, and in case of a difference of opinion, the third reviewer was consulted to sort it out. The case reports included were those dealing exclusively with human subjects, were published in the English language and had free, full-text, public access.

Quality assessment was done using Joanna Briggs Institute's (JBI) Critical Appraisal Checklist for Case Reports²⁵ (Table 1). Data was extracted and the case

Table-1: Quality assessment of the case reports analysed.

Author	Outcome	1	2	3	4	5	6	7	8
Sučić et al. ¹⁹	YES	NO	YES	YES	YES	YES	YES	NO	YES
Huang et al. ²⁰	YES	NO	YES	YES	YES	YES	YES	NO	YES
Kim et al. ²¹	YES	NO	YES	YES	YES	YES	YES	NO	YES
Vyas et al. ²²	NO	NO	YES	YES	YES	NO	NO	NO	YES
Sehgal et al. ²³	YES	NO	YES	YES	YES	YES	YES	NO	YES

1: How well-defined were the patient's demographic details? 2: Did the patient's history make sense and was it presented as a timeline? 3: Was the patient's clinical state at the time of presentation adequately described? 4: Were the techniques and outcomes of any diagnostic tests or evaluations fully explained? 5: Was the intervention or treatment method explained in detail? 6: How well was the clinical situation described after the intervention? 7: Have unpleasant or unexpected events been named and described? 8: Does the case report offer actionable advice?

JBI: Joanna Briggs Institute

aspiration should help in the definitive MM diagnosis¹⁸.

The incidence of simultaneous diagnosis of prostate cancer and lymphoid malignancies is reported to be approximately 1.2% but synchronous occurrence of prostate adenocarcinoma and MM is only reported in a few cases, where the diagnosis was challenging.¹⁹⁻²³ In a metachronous setting, the treatment of one cancer can easily mask the symptoms of second tumour, especially with bone remodelling agents, and present a diagnostic dilemma. To the best of our knowledge, very few studies have been done related to the coexistence of MM and

reports were evaluated for demographic, diagnostic and treatment parameters.

Results

Of the 515 studies initially identified, 5(0.97%) were analysed (Figure). All the patients were males with mean age 68.6±10.78 years. The most common symptom reported at presentation was lower back pain (LBP) 3(60%), urinary symptoms 2(40%), radiation of pain in both legs 2(20%), and tingling sensation of the left gluteal region and thigh 1(20%), while symptoms were not reported in 2(20%). Osteolytic lesions were seen in 4(80%)

Table-2: Results of the case reports

Author	Patient details (age, sex, and demographics)	Symptoms at presentation	Haemoglobin	Serum Creatinine	Bone Marrow biopsy	Histopathology of Prostate	Imaging	Treatment	Outcome
Sučić et al. 19	63 years, male, not mentioned	N/A	N/A	N/A	Increase in plasma cells, metastases and clusters of malignant cells found	Adenocarcinoma was found. Infiltrative small glands arranged with a single cell layer of polymorphic carcinoma cells. Cribriform atypical glands and signet-ring cells were also seen.	X-ray of the spine showed several Osteolytic lesions	Dexamethasone plus thalidomide	Fourteen months after diagnosis of MM, the patient died because of prostate cancer spread.
Huang et al. 20	77 years, male, not mentioned	N/A	N/A	N/A	Plasma cells replacing the normal bone marrow cells	Adenocarcinoma of the prostate with the invasion of the capsule and perineural involvement.	A nuclear bone scan showed moderate to severe degenerative changes. CT scan showed lucency and sclerosis of the axial skeleton. MRI showed a lobular pattern of diffuse bone marrow replacement.	Hormonal therapy and Radiotherapy	Twenty months after completion of the treatment, the patient's PSA level had decreased
Kim et al. 21]	58 years, male, not mentioned	Lower back pain and tingling sensation of the left gluteal region and thigh. The patient also complained of urinary symptoms, including hesitancy, mild voiding difficulties, and residual urine sensation.	12.5g/dl	1.0mg/dl	Plasma cell neoplasm	Adenocarcinoma of Prostate	Spinal MRI showed an osteolytic lesion with cortical pinning on the left half of the vertebra L3. The left transverse process was involved too.	Radiation therapy, Bicalutamide, Goserelin, bisphosphonates and amitriptyline	The patient survived with no tumour recurrence
Vyas et al. 22	83 years, male, not mentioned	Low back pain and urinary incontinence	8.6g/dl	Normal (Value not mentioned)	Sixty five percent plasma cells arranged in sheets and clusters	Adenocarcinoma of prostate	MRI showed osteolytic lesions in the skull and vertebrae	N/A	N/A
Sehgal et al. 23	62 years, male, not mentioned	Low back pain and radiation of pain to both legs	9.6g/dl	1.2 mg/dl	Infiltration of bone by malignant epithelial cells, twelve percent plasma cells on aspirate smears	Adenocarcinoma of prostate	Multiple lytic lesions in the skull on skeletal survey	Vincristine, Endoxan, Prednisolone, Melphalan, Prednisone and Leuprolide.	The patient showed decrease in lytic bone lesion

CT: Computed tomography, MRI: Magnetic resonance imaging, PSA: Prostate surface antigen, Normal haemoglobin level: 13.8-17.2 g/dl, Grade 1 thrombocytopenia: 75-150 × 109/l, Grade 2 thrombocytopenia: 50-75 × 109/l, Grade 3 thrombocytopenia: 25-50 × 109/l, Grade 4 thrombocytopenia: <25 × 109/l, Normal serum calcium: 8.6-10.3mg/dl, Normal serum creatinine: 0.7-1.3mg/dl.

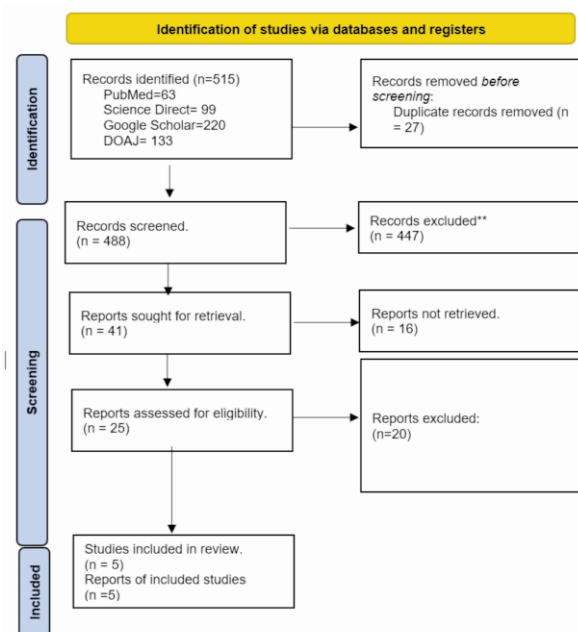


Figure: Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) flowchart.

patients on imaging with elevated prostate surface antigen (PSA) levels and prostate adenocarcinoma confirmed on biopsy. Anaemia was found in 3(60%) patients, while in 2(40%) cases it was not reported. Further, 2(40%) patients had thrombocytopenia, 2(40%) had normal platelet count and 1(20%) case was not reported. Hypocalcaemia was found in 1(20%) patient, 2(40%) had normal calcium level, and 2(40%) cases were not reported. Finally, 3 (60%) patients had normal serum creatinine levels, while it was not reported in 2(40%) cases (Table 2).

Discussion

Except for the patient mentioned by Huang et al.²⁰, who had PSA 12ng/ml, findings of moderate to severe degenerative changes on nuclear bone scan, lucency and sclerosis of the axial skeleton on computed tomography (CT), and a lobular pattern of diffuse bone marrow replacement on magnetic resonance imaging (MRI), 4 out of 5 patients in the case reports reviewed had the presence of osteolytic lesions along with elevated PSA levels. This is a noteworthy exception because extensively metastatic prostate cancer with imaging characteristics comparable to those of this patient would often result in a PSA of much greater than 12ng/mL. In cases where there are numerous metastases, like the one described by Huang et al., a relatively lower PSA level may point to conditions like high-grade poorly differentiated or de-differentiated prostate adenocarcinoma, small cell

carcinoma, neuroendocrine tumour, or MM²⁰. Huang et al. also noted a two-month delay in MM diagnosis because the patient received hormonal therapy for probable prostate cancer with metastases rather than MM. The patient's PSA level dropped to 0.1ng/mL after two months of hormonal therapy, but the follow-up MRI bone scan revealed no significant changes from the initial findings and was consistent with extensively metastatic cancer. A bone marrow biopsy later indicated that the patient had MM²⁰.

Anaemia was the most common finding in the initial blood count followed by thrombocytopenia in the current review. Anaemia is the second most common finding in MM patients after a skeletal lytic lesion. At the time of MM diagnosis, 70% patients have anaemia, with a median haemoglobin (Hb) level of 10.5g/dL²⁶. According to staging guidelines²⁷, the severity of anaemia determines the disease's stage and prognosis. The anaemia associated with MM is typically normochromic and normocytic and is characterised by a reduction in the time that erythrocytes can survive after being formed and a failure of the bone marrow to compensate for the increased red blood cell (RBC) production. These potential mechanisms for the decline in RBC generation in MM include decreased storage iron availability, inadequate erythropoietin (EPO) response to anaemia level, and cytokine overproduction that stops erythropoiesis tumour necrosis factor (TNF), interleukin-1 (IL-1) and IL-6. These are the cytokines that may reduce the use of iron reserves from reticuloendothelial cells and may prevent the kidney from producing EPO. Additionally, they directly suppress the growth of erythroid precursor cells²⁸.

The primary cause of anaemia in MM is related to poor RBC production by the bone marrow as a result of myeloma cells invading and replacing healthy bone marrow cells, as well as bone marrow suppression as a side effect of chemotherapy. However, EPO production is impaired, or erythroid precursor cells are less responsive to EPO, which is the primary cause of the diminished RBC production²⁹.

Although anaemia associated with metastatic prostate cancer is a frequent occurrence, the precise incidence of this anaemia can only be inferred from the limited data. A subset of patients who underwent bilateral orchiectomy for prostate cancer experienced moderate anaemia in 78% cases, with Hb fall of 1g/dL or less from baseline levels, and 29% cases showed a decline of 2g/dL or higher³⁰. Similar findings show that anaemia is present at diagnosis in about 30% prostate cancer patients with bone metastases^{33,32}.

On initial blood tests, thrombocytopenia was the second most typical finding. MM usually exhibits thrombocytopenia, but it is rarely severe enough to result in bleeding³³. In patients with dysproteinaemias, bleeding has been linked to platelet dysfunction and has been documented³⁴⁻³⁶. For the purpose of elucidating the relationship between paraproteinemia and bleeding, Herbert et al. evaluated 62 patients, and discovered elevated levels of specific paraproteins that caused obvious bleeding³⁵. According to their findings, 36% cases of macroglobulinaemia had bleeding as a major issue. IgG myeloma had a lower incidence of bleeding (13%) than IgA myeloma (33%). In virtually all cases, the kappa light chain was more often associated with bleeding, demonstrating that bleeding was connected to molecule size rather than structure³⁵. However, none of the thrombocytopenia patients in the current review made a bleeding presentation. In individuals with metastatic prostate cancer, skeletal metastasis is a common consequence that may already be present at the time of initial diagnosis^{37,38}. Anaemia and thrombocytopenia may arise from impaired bone marrow function, which depends on how far the metastatic cells have gone^{39,40}. Nieder et al. performed a retrospective cohort study involving all men who received treatment for prostate cancer with bone metastases. Among them, 33% patients, or 5 out of 15, experienced severe thrombocytopenia. These patients also needed blood transfusions. One to four months, with a median of 2.5 months, passed between a Hb level <10g/dL and a thrombocyte count <50 x 10⁹/L. The survival was <4 months even with platelet transfusion. Patients who did not initially have a thrombocyte level <50 x 10⁹/L did not experience any bleeding events⁴¹.

LBP was the most common symptom reported in the current review. Back pain is the second most common complaint, after upper respiratory infection, in primary care setting⁴². However, only 0.7% patients who presented with back pain had a malignant cause⁴³. A retrospective population-based study by Goldschmidt et al. showed that 58% MM patients complained of back pain before MM diagnosis⁴⁴. Similarly, Schaberg et al. showed that 64% patients with spinal metastases reported back pain. Back pain was described in 93% of the cervical, 43% of the thoracic, and 76% of lumbosacral spine metastases. Schaberg et al. also reported that metastatic prostate cancer accounted for 20.1% of spinal metastases⁴⁵.

In the current review, urinary incontinence was the second most typical symptom at presentation. In addition to sensory or motor paralysis, faecal incontinence, and

perianal anaesthesia, urinary incontinence is regarded by the National Institute for Health and Care Excellence (NICE) as one of the warning signs of spinal cord or cauda equina compression⁴⁶. Also, 5% MM presentations are caused by spinal cord compression after vertebral compression fractures or vertebral plasmacytomas^{47,48,49}. Similar symptoms and signs of spinal cord compression were seen in an MM case reported by Chakrabort et al⁵⁰. Despite the fact that all patients in the current review initially complained of urine incontinence, none of them exhibited spinal cord compression. It is understood that tumour growth in males with prostate cancer may cause urine incontinence, but the literature lacks information on this crucial topic. Based on a questionnaire survey, a Danish study revealed an incontinence rate of 27%. In that study, 71 men with localised prostate cancer were followed up for a median of 3.3 years⁵¹. However, the definition of incontinence was rather rigorous as it included even dripping or seeping. This could be a valid justification for the rise in prevalence. The prevalence of incontinence in men rises with age, according to data from Austria. Men aged 70 years and older reported incontinence episodes at a rate of 15.6%, but prostate cancer appeared to be linked to a greater incontinence rate that is difficult to explain by ageing alone⁵².

One patient in the current review had hypocalcaemia with a corrected calcium level of 8.2mg/dl. This finding is of significant importance as in malignancy, hypercalcaemia is more common than hypocalcaemia and may occur in up to 30% of patients and usually indicate advanced disease and poor prognosis⁵³. In contrast, cancer is not known to be linked to hypocalcaemia. Two studies that looked at the prevalence of hypocalcaemia in cancer patients and included patients over the age of 25 years had wildly divergent findings because of the different patient populations analysed; 1.6% of 7625 ambulatory oncology patients were hypocalcaemic in one study⁵⁴, while the other found an incidence of 10.8% in hospitalised patients⁵⁵. Riancho et al. reported an incidence of 5-13% in patients with solid tumours and bone metastases⁵⁶. The difference depends on the calculation of corrected total calcium value as serum albumin concentrations are reduced in cancer patients⁵⁷.

In the current review, 3(60%) patients had normal serum creatinine levels, while 2(40%) cases were not reported. This finding is unique as kidney involvement is seen in up to 50% MM cases⁵⁸. It can be identified at presentation or during the course of the disease. There is an indication for the investigation of MM in any unexplained kidney disease. The pathology is heterogeneous in nature with a

variety of mechanisms of pathogenesis⁵⁸. Many factors contribute to myeloma kidney disease and the most frequent is the deposition of monoclonal Igs or fragments with the presentation of cast nephropathy^{58,59}. A serum creatinine value of 2mg/dL is used to define the presence of renal dysfunction in newly diagnosed patients with MM in most studies⁶⁰. Similarly, serum creatinine as a prostate cancer staging and prognostic marker has been examined in several clinical investigations⁶¹⁻⁶⁷. For example, serum creatinine levels predicted advanced stage of prostate carcinoma and decreased survival of patients in one study⁶¹ and were increased in patients presenting with high PSA and locally advanced or metastatic disease compared to those with low PSA initially⁶⁰. In a group of men with prostate cancer that was hormone-resistant, an increase in serum creatinine was also associated with decreased survival⁶².

The prevalence of MM and prostate cancer simultaneously in the current review was found at an average age of 63 years. Jahn et al. observed a marked age-related increase in the prevalence of incidental prostate cancer discovered at autopsy with a prevalence of 47.3% among white United States and European men aged above 80 years⁶⁸. Similarly, MM is a malignancy of older adults with the median age at diagnosis being 69 years in the US. Over 60% of diagnoses are made in those older than 65 year, and less than 15% in those aged <55 years to 69 years. Based on the prevalence of occult prostate cancer in older man in Caucasian population, as reported by Jahn et al. it can be hypothesised that in a subset of MM patients diagnosed at age >65 years, occult prostate cancer prevalence will be much higher and hence the incidence of coexistence of these two tumours would be much higher than currently estimated. However, this needs to be proved with a much larger sample of population to get statistically significant results. Despite the predicted increase in the prevalence of prostate cancer in the elderly, most studies investigating optimal treatment regimens have focussed on men aged <75 years⁷⁰. Prospective studies investigating the utility of prostate cancer screening excluded patients aged >75 years^{71,72}. Likewise, the US Preventive Services Task Force (USPSTF) explicitly recommends against screening men aged 75 years or older. Yet, this statement is based in large part on extrapolations from studies of patients aged <75 years and does not account for health status or comorbidities⁷³. Therefore, even if the incidence of coexistence of MM and prostate cancer seems to be much higher, the coexistence in 2 of the 5 case reports seems to have no clinical significance in the sense that majority of patients of prostate cancers aged >75 years never get or become eligible for any treatment.

Although genetic events appear to play a key role in the initiation and progression of plasma cell myeloma, the bone marrow (BM) microenvironment factors, like extracellular matrix proteins, secreted cytokines and growth factors, and interaction of the BM stromal cells, are also important in pathogenesis and progression of MM⁷⁴. It is also interesting that microenvironment in prostate cancer and MM showed important similarities and that certain cytokines were involved in neoplastic transformation and clinical course of both the diseases⁷⁴. IL-6, an essential activating growth factor and antiapoptotic agent of MM, is also essential in signalling the mitogen-activated protein kinase pathway in prostate cancer⁷⁵. Insulin-like growth factor 1 (IGF-1) is also a potent growth factor that increases proliferation of MM plasmocytes and is also involved in the progression of prostate cancer⁷⁶. Vascular endothelial growth factor (VEGF), secreted by some myeloma cell lines, is an important mediator of angiogenesis in MM and prostate cancer⁷⁷. Stromal-derived factor 1 (SDF-1) was found to be a chemoattractant factor causing the selective adhesion of myeloma cells to the bone, enhancing their proliferation. SDF-1 was also shown to be a chemoattractant for metastasis of prostate cancer cells to the bone⁷⁸. Thus, it may be possible that the development of MM as a secondary malignant disease enhanced the progression of prostate cancer and metastasis to the bone, but till date it has not been confirmed by larger studies with bigger sample size.

The current systematic review has its limitations, as it included only case reports, skipping clinical trials and observational studies that provide authentic sources of data. Case reports lack internal validity and any conclusion drawn from them needs to be verified by observational studies and clinical trials. The coexistence of prostatic tumour with MM is rare and the current review had a sample size of only 5 patients and that has reduced the power of the analysis. The ethnicity of the patients was missing in all case reports. It is important to mention ethnicity of the patients because it helps in evaluating the prevalence of disease in a particular population. Therefore, original studies must include complete demographic characteristics and genetic prevalence in future studies.

Conclusion

Although very rare, the coexistence of MM and prostate cancer has been demonstrated by the case reports reviewed. Therefore, consideration of MM as a possible differential diagnosis, even if seemingly unlikely, in the case of osteolytic bony lesions with the presence of elevated PSA is of great importance to prevent diagnostic

delay. Clinical characteristics in the coexistence of both diseases may differ on a case-by-case basis, and, therefore, physicians should report such cases to add to the existing literature. As prostate cancer occurs almost exclusively in males, further epidemiological and genetic studies on a larger scale are needed to confirm and clarify the coexistence or an association between the two.

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