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Severe Pancytopenia After COVID-19 Revealing a Case of Primary Bone Marrow Diffuse Large B Cell Lymphoma

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Male, 80-year-old
Final Diagnosis: COVID 19 infection • primary bone marrow diffuse large B cell lymphoma
Symptoms: Fatigue • fever • weight loss
Medication: —
Clinical Procedure: Bone marrow biopsy
Specialty: Hematology • Infectious Diseases • Oncology

Objective: Rare disease

Background: Diffuse large B cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL). While bone marrow (BM) involvement is common in lymphoma, primary bone marrow (PBM) DLBCL is extremely rare. We present a case of PBM DLBCL discovered in a patient with COVID-19.

Case Report: An 80-year-old man presented with generalized abdominal pain, weight loss, fever, fatigue, anorexia, and watery diarrhea over a 3-month period. Physical examination was unremarkable. Laboratory workup revealed anemia, thrombocytopenia, and elevated inflammation markers. SARS-COV-2 PCR was positive, while blood cultures were negative. A rapid decline in the white blood cell count in the following days prompted a BM biopsy, confirming the diagnosis of PBM DLBCL. Computed tomography (CT) did not show thoracic or abdominal lymphadenopathy. The patient received packed red blood cell and platelet transfusions, granulocyte colony-stimulating factor (G-CSF) for pancytopenia, and empirical antibiotics for suspected infection. Due to active COVID-19 and advanced age, cytotoxic chemotherapy was delayed. Rituximab and prednisone were initiated on day 9, followed by an infusion reaction, which led to treatment discontinuation. He died 2 days later.

Conclusions: Diagnosing PBM malignancy is challenging, especially with coexisting infection. It is essential to suspect underlying BM malignancy in patients with clinical deterioration and worsening pancytopenia despite adequate treatment. The diagnosis of PBM DLBCL requires the absence of lymphadenopathy, and the presence of histologically confirmed DLBCL. Prompt management with combination chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) with/without hematopoietic stem cell transplant can improve the prognosis.

Keywords: COVID-19 • Lymphoma, Non-Hodgkin • Pancytopenia • Rituximab

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/937500

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Background

Non-Hodgkin lymphoma (NHL) accounts for about 4% of cancers diagnosed every year in the United States [1]. Diffuse large B cell lymphoma (DLBCL) is the most common subtype, accounting for 25% of NHL [1-3]. Genetic alterations in the B cell leukemia or lymphoma 2 (BCL2), BCL6, and MYC genes have been associated with DLBCL [4,5]. Risk factors of DLBCL (and NHL) include chronic immunodeficiency, Human Immunodeficiency Virus (HIV) infection, Epstein-Barr Virus (EBV) infection, immunosuppressive therapy, chemotherapeutic agents, radiation, and auto-immune diseases [6-8]. While secondary bone marrow (BM) involvement is common in lymphoma [9], primary bone marrow (PBM) DLBCL is extremely rare [10-13]. We present a case of an 80-year-old man with a recent history of iron deficiency anemia and thrombocytopenia who presented with fever, fatigue, weight loss, chronic diarrhea, and abdominal pain, and was found to have worsening pancytopenia with concurrent COVID-19. The diagnosis of primary bone marrow (PBM) DLBCL was made.

Case Report

History of present illness

An 80-year-old man presented with generalized abdominal pain and an undetermined weight loss over a 3-month period. He described his pain as generalized, vague, and unrelated to food intake. He endorsed fevers (but denied night sweats), fatigue, anorexia, and watery diarrhea, over the same time period.

Past Medical History

Our patient was a former smoker (he quit 13 years before). He had a past medical history of diabetes mellitus, hypertension, major depressive disorder, chronic SIADH likely from Trazodone, and mild chronic normocytic anemia for 20 years. No risk factor of immunodeficiency was reported. Six years prior, diagnostic workup for the anemia, including eso-gastroduodenoscopy (EGD) and colonoscopy, was inconclusive. One month prior, he was admitted in another hospital for iron deficiency anemia and thrombocytopenia (**Table 1**). A full endoscopic examination was performed and showed an erythematous antral mucosa on EGD, and sessile polyps and hemorrhoids on colonoscopy. Antral histology revealed chronic gastritis with intestinal metaplasia, without evidence of malignancy. Capsule endoscopy of small bowel and computed tomography (CT) enterography were unremarkable. He was discharged with iron supplementation and outpatient follow-up with Hematology.

Physical Exam

On initial evaluation, our patient was afebrile (36.7°C) and tachycardic (110 beats/min), with otherwise normal blood pressure, respiratory rate, and oxygen saturation. His weight was 62.2 kg (137.1 lbs.), with a body mass index (BMI) of 21.5 kg/m^2, representing a 9.6 kg loss from a previously recorded weight 5 months prior. He appeared cachectic, without scleral icterus. Chest auscultation revealed regular tachycardia without murmurs, with clear lungs on auscultation. The abdomen was soft and nontender, without palpable hepatomegaly or splenomegaly. No peripheral lymphadenopathy, rash, or lower-extremity edema were appreciated.

Investigations

Laboratory results are summarized in **Table 1**. A complete blood count (CBC) on day 1 showed bicytopenia with microcytic anemia, thrombocytopenia, and a normal white blood cells (WBC) count, with a normal absolute neutrophil count (ANC) of 3.92×10^3/uL, normal lymphocyte count, and eosinopenia. His reticulocyte index was 0.81 (adequate response ≥2). LDH was 2058 U/L (N: 135-225 U/L). An elevated C-reactive protein (CRP) at 207 mg/L (N: <10 mg/dL) and procalcitonin (PCT) at 2.07 (≤0.08 ng/mL) raised the concern for infection. Further workup showed negative blood cultures and fungal testing (1,3 Beta-D-Glucan), and a positive SARS-CoV-2 PCR. A rapid decline of the WBC (ANC of 0.13×10^3/uL) within 5 days of admission raised the concern for a primary bone marrow condition, likely complicated by sepsis secondary to SARS-COV-2 infection. A peripheral smear showed microcytic hypochromic red blood cells (RBCs), nucleated RBCs, and atypical lymphocytes, but no immature cells. BM aspiration and biopsy were performed, and results were obtained on day 9 of admission. Histology revealed DLBCL with more than 90% BM involvement. The residual BM exhibited trilineage maturation, with an overall cellularity 50-80%, a number of blasts <5%, mild diffuse marrow fibrosis (MF-1), and detectable iron storage (**Figure 1**). Flow cytometry of the BM showed 13% of clonal B cell proliferation with positive Kappa and CD20, and negative CD5 and CD10 (**Figure 2**). Immunohistochemistry (IHC) revealed >90% of CD20 highlights, without increase in the blast population. A cytogenetic study showed a normal male karyotype (**Figure 3**). Fluorescence in-situ hybridization (FISH) ruled out c-MYC, BCL-2/IGH (translocation t(14;18)) or BCL-6 rearrangement (**Figure 4**). A pan CT scan did not reveal lymphadenopathy of significance or any masses/organomegaly, and showed bibasilar atelectasis, without lung infiltrates. The diagnosis of PBM DLBCL was made. HIV 1,2 antigen/antibody test and EBV PCR returned negative. Pre-therapeutic testing for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), and hepatitis C antibody was negative. The International Prognostic Index (IPI) was 4, predicting a poor prognosis.

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Table 1. Complete blood count (CBC). The bicytopenia found at the patient's previous admission progressed into pancytopenia in the setting of COVID-19. Note that the patient had normocytic anemia and thrombocytopenia 1 month prior to admission.

	Range & unit	2 months prior (Baseline)	1 month prior (previous admission)	Day 1	Day 3	Day 5	Day 7	Day 9	Day 11
Platelets	150-450×10^3/mcL	227	119	143	77	53	21	13	12
White blood cells	4.80-10.80×10^3/mcL	6.74	6.54	8.00	2.65	1.84	0.63	0.42	0.37
Red blood cells	4.70-6.10×10^6/mcL	4.10	3.21	3.18	2.62	3.66	2.81	2.19	2.51
Hemoglobin	14.0-18.0 g/dL	11.4	8.7	8.1	6.5	9.3	7.2	5.6	6.4
Hematocrit	42.0-52.0%	34.8	25.2	24.1	20.0	28.2	22.0	18.0	19.3
MCV	80.0-99.0 fL	84.9	78.5	75.8	76.3	77.0	78.3	82.2	76.9
MCH	27.0-31.0 fL	27.8	27.1	25.5	24.8	25.4	25.6	25.6	25.5
RDW	12.0-15.0%	13.8	15.2	17.1	17.2	17.2	17.2	17.3	17.4
Neutrophils	44.0-70.0%	64.5	47.2	48.9	49.5	22.3	6.4	11.8	16.2
Lymphocyte	20.0-45.0%	24.2	24.3	29.8	34.7	64.1	76.2	78.6	70.3
Monocyte	2.0-10.0%	22.8	27.1	20.0	14.7	10.9	9.5	4.8	8.1
Eosinophil	1.0-4.0%	0.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Basophil	0.2-1.8%	0.4	0.5	0.3	0.0	1.1	0.0	0.0	0.0
Immature granulocytes	0.0-0.2%	0.7	0.9	1.0	1.1	1.6	7.9	4.8	5.4

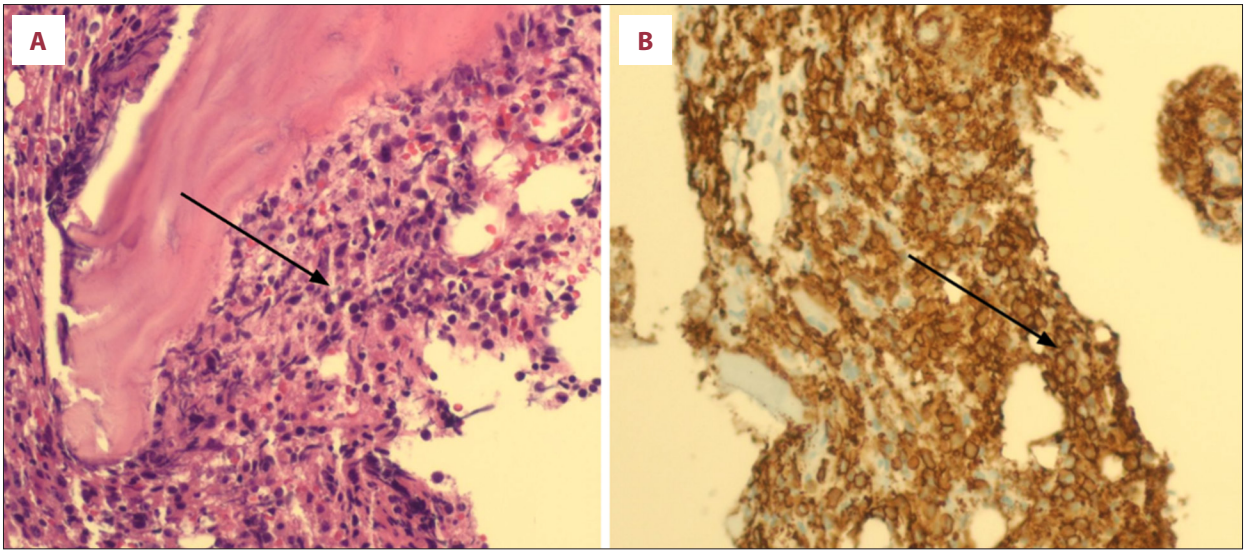

Figure 1. Bone marrow (BM) histology showing large B cell lymphoma cells with diffuse BM involvement >90% BM on hematoxylin/eosin stain (200×, see image **A,** black arrow), with positive staining for antibodies to CD20 (200×, see image **B,** black arrow).

Treatment and Follow-Up

Our patient was initially managed conservatively for COVID-19. He was treated with empirical antibiotics for a suspected bacterial infection. He received 1 unit of packed red blood cell (pRBC), 1 unit of platelets, and granulocyte colony-stimulating factor (G-CSF) for pancytopenia. Despite these interventions, his clinical condition continued to deteriorate progressively, with an Eastern Cooperative Oncology Group (ECOG) score of 4, progressively worsening altered mental status, and decreasing leukocyte count (**Table 1**). Once the diagnosis of PBM DLBCL was made on day 9 of admission, the decision was made to treat with a combination chemotherapy, including rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone

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Antibody	Description	Results
B-cell associated		
CD19	Pan B-cell antigen	6.92%
CD20	Pan B-cell antigen	10.72%
CD10	Follicle center B-cells, CALLA, myeloid subset	0.47%
CD11c	Monocytes, myeloid subset, hairy cell leukemia	14.22%
CD23	Mature B-cells, CLL	1.40%
CD22	Pan B-cell antigen	12.24%
CD25	Acvtivated T and B-cells, hairy cell leukemia	18.55%
CD71	Transferrin receptor, activation antigen	4.75%
CD81	B-cells	8.03%
CD103	Activated cells, hairy cell leukemia	3.82%
CD200	B-cells	3.90%
Kappa	Kappa Ig light chain, B-cells, plasma cells	3.50%
Lambda	lambda Ig light chain B-cells, plasma cells	1.71%

Antibody	Description	Results
Myeloid associated		
CD11b	Mature myeloid cells, NK cells and T-cell subset	7.78%
CD13	Myeloid cells, monocytes	12.97%
CD14	Mature monocytes	3.23%
CD15	Granulocytes	8.11%
CD16	Granulocytes, NK cells	8.19%
CD33	Myeloid cells, monocytes	7.50%
CD64	Monocytes	8.27%

Figure 2. Flow cytometry. Trace B cell population exhibiting bright CD20, K LC excess, and increased forward scatter angle (<1% cellularity). Monocytes are relatively increased (~13% with a subset showing abnormal loss of CD14). No evidence for an acute leukemia or T cell lymphoproliferative disorder.

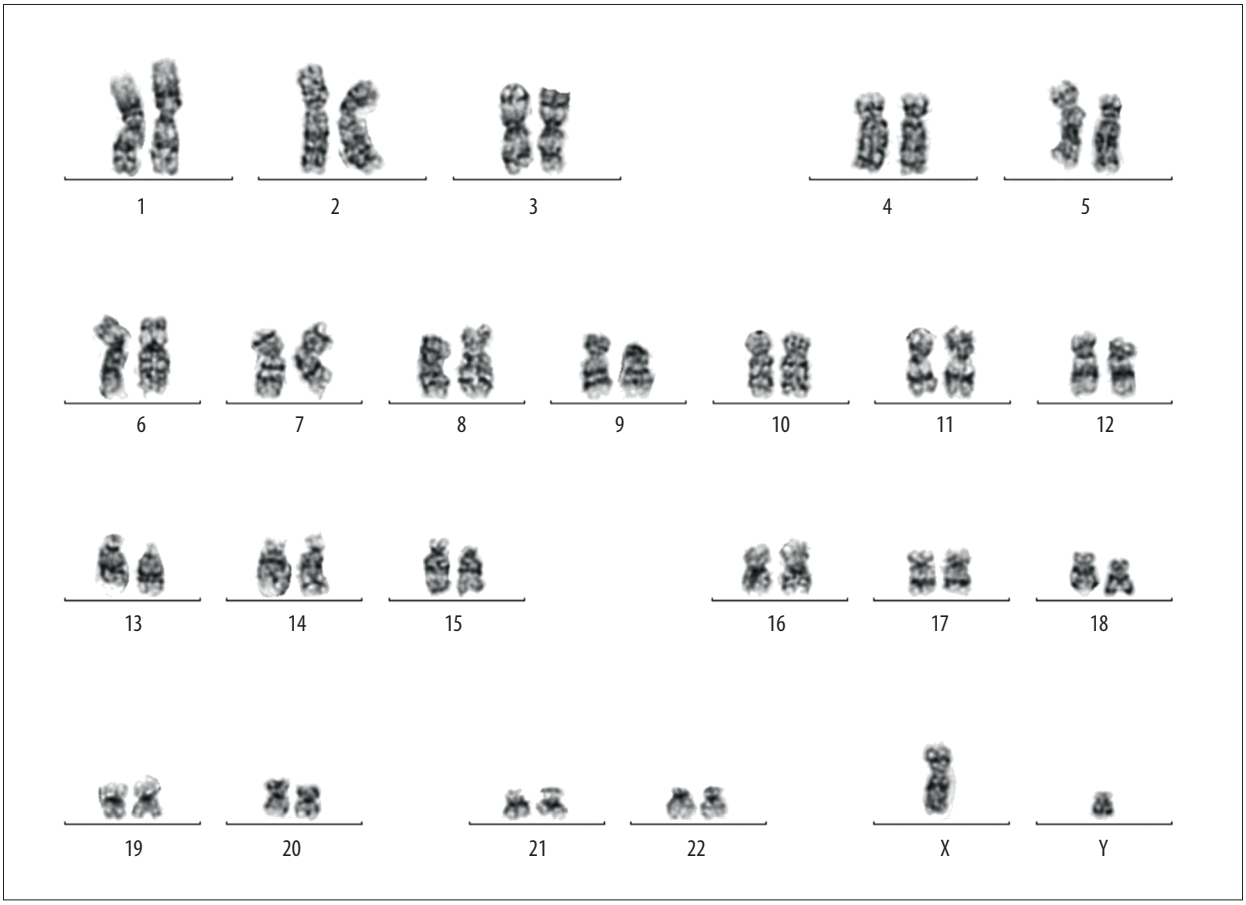

Figure 3. Karyotyping of B cells in the bone marrow. A normal male karyotype was observed in 18 metaphase cells analyzed.

(R-CHOP), along with G-CSF. However, given the patient's active COVID-19 and advanced age, cytotoxic chemotherapy was reserved for a later time. Rituximab (375 mg/m^2) and Prednisone 80 mg were started on day 10. Minutes after the first dose of rituximab, the patient developed an infusion reaction. Rituximab was held, and the patient was treated with chlorpheniramine and solumedrol. Further discussions with the patient and his family members led to the decision to keep the patient on palliative care. He was treated with morphine, then became hypotensive despite fluid infusions, and died 2 days after stopping therapy.

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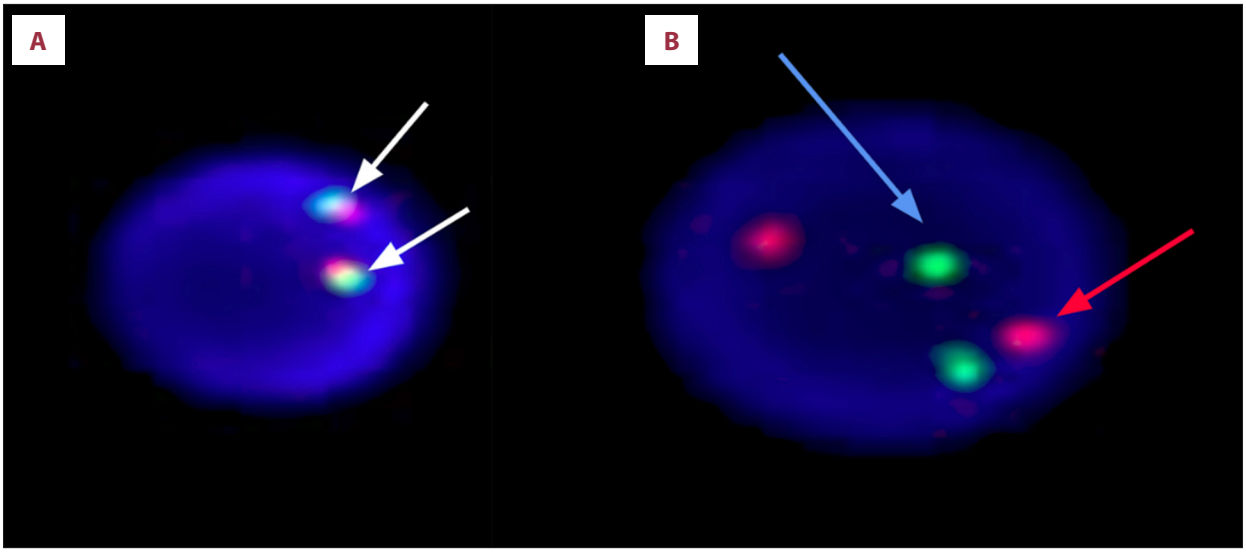

Figure 4. Fluorescence in situ hybridization (FISH) study showing a normal nucleus. Screening for MYC break rearrangement (MYC-BA) using the XT MYC BA probe showed two orange/green fusion signals, indicating a negative study (see image **A,** white arrows). The IGH/BCL2 probe was used to detect t(14;18) translocation. Two green signals (IGH) (see image **B,** blue arrow) and two orange signals (BCL2) (see image **B,** red arrow) indicate a negative test result for t(14;18) translocation.

Discussion

DLBCL is currently the most common lymphoid neoplasm [14,15], accounting for 25% of NHL worldwide [3,16]. PBM lymphoma is a rare disease, and PBM DLBCL is the most common subtype [10,11,13]. DLBCL has a male predominance, with median ages ranging from 57 to 64 years according to the literature [10,17].

While BM involvement is common in lymphoma [9], PBM DLBCL is extremely rare [10-12]. PBM lymphoma can present with isolated anemia, thrombocytopenia, bicytopenia, or pancytopenia, due to bone marrow infiltration and/or auto-immune destruction [10,18-21]. In a case series by Chang et al of 12 patients with DLBCL, only 1 presented with isolated BM involvement, and most patients initially presented with anemia and thrombocytopenia [10]. In our patient, we believe that the COVID-19 precipitated the pancytopenia; in fact, several cases of COVID-19-induced pancytopenia have been described in the literature, including in patients with underlying hematologic malignancy [22-26].

Currently, there are no evidence-based diagnostic criteria for PBM DLBCL. Positron emission tomography (PET) scanning was not performed in our patient. It can be useful for diagnosis, but there are no guidelines for the diagnosis of PBM DLBCL using PET [27]. Several authors have proposed diagnostic criteria for PBM DLBCL. According to Chang et al, the diagnosis requires the absence of lymphadenopathy on whole-body CT scan or physical examination, the presence of histologically confirmed BM involvement with DLBCL, and CD19 or CD20 expression on IHC or flow cytometry [10]. No specific chromosomal abnormalities or other CD markers have been associated with PBM DLBCL [12,28]. CD5 expression in PBM DLBCL is variable in the literature, ranging from 0% to 80% of PBM DLBCL cases [5,10,12,28], and its clinical significance remains uncertain. CD30 was seen in 25% and carries a favorable prognosis [5].

Several reports showed complete remission of PBM DLBCL following chemotherapy with R-CHOP with/without hematopoietic stem cell transplant [10,27,29,30]. Almost all cases of PBM DLBCL have a high IPI, predicting low survival rates [31,32]. The median survival was found to be less than 9 months [31].

Our patient had a 1-month history of bicytopenia, and presented with worsening pancytopenia following COVID-19, likely due to reduced BM reserve caused by the PBM DLBCL. The diagnosis of PBM DLBCL was made, and our patient tested negative for HIV and EBV. He had a high IPI score, indicating a poor prognosis. Following an infusion reaction to rituximab, the treatment was held, and he died a few days later from a cardiac arrest.

Conclusions

The diagnosis of PBM DLBCL can be challenging, especially in patients with concomitant infection. In cases of clinical deterioration and worsening pancytopenia despite adequate management, clinicians should have high clinical suspicion of BM malignancy and perform a prompt diagnostic workup for PBM malignancy. PBM DLBCL is an aggressive malignancy, but

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the prognosis improves with timely management with rituximab-based chemotherapy and/or hematopoietic stem cell transplantation.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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