Peripheral monoclonal plasmacytosis in infective endocarditis: a tangled web

A 56-year-old man with suspected infective endocarditis and sepsis was admitted to the cardiology department. His medical history included arterial hypertension treated with ACE inhibitors and valvular heart disease, with an aortic bioprosthetic replacement performed 16 years earlier. He was initially treated with empirical daptomycin and ceftriaxone, with improvement in C-reactive protein and procalcitonin value, but persistent thrombocytopenia and hyperleukocytosis with atypical cells were flagged by the blood cell counter. Multicolor flow cytometry (MFC) revealed 22% circulating κ light chain-restricted $CD38^+$ $CD138^+$ $CD19^+$ $CD45^+$ $CD56^-$ plasma cells (PC) (Figure 1), while B-cell lymphocytes were found to be polyclonal. The patient was therefore referred to our department presenting with persistent fever, chills, asthenia and lower back pain. On physical examination, splinter hemorrhages were noted. Blood tests revealed hyperleukocytosis (leukocytes 22.7×10^9/L, neutrophils $18\text{x}10^9$/L, monocytes $1{,}5\times10^9$/L), mild normocytic anemia (hemoglobin 11.2 g/dL), severe thrombocytopenia ($21{,}000\text{x}10^9$/L), renal impairment (serum creatinine 2.07 mg/dL), high inflammation markers (C-reactive protein 68.6 mg/L and procalcitonin 3.04 μg/L) and high NT-proBNP 7543 ng/L. Two distinct IgM-κ paraproteins (1.4 g/L and 2.5 g/L) were detected, κ free light chain was 54.21 mg/L, λ free light chain 29.86 mg/L (ratio=1.81); urine analysis revealed proteinuria (619 mg/day) with negative urine immunofixation. Consecutive blood cultures (including those for the HACEK group) and serum β-D-glucan tests were negative. Empiric minocycline was added to the antimicrobial therapy, and dexamethasone 40 mg daily for 4 days was administered to provisionally manage the suspected plasma cell dyscrasia. Extensive instrumental tests were performed: transesophageal echocardiography (TEE) showed fibrosclerotic degeneration and severe stenosis of the bioprosthetic aortic valve, as well as a periprosthetic abscess at the mitral-aortic junction (8 mm in thickness and 23 mm in length; Figure 2). Fundoscopic examination revealed no abnormalities. Computed tomography (CT) scan with contrast revealed multiple septic emboli in the spleen and kidneys (the largest lesion measuring 13 mm on the inferior pole of the right kidney) and an intramuscular hematoma in the psoas muscle, which could explain the lumbar pain.

To complete the hematologic assessment, a bone marrow aspirate, a trephine biopsy, and an additional MFC on peripheral blood were performed. Surprisingly, 5 days after the first abnormal detection, no more monoclonal PC were found, either in the peripheral blood (0.4% polyclonal PC) or in the bone marrow aspirate (0.3% PC with predominance of κ expression without monoclonality). Similarly, the trephine biopsy showed polyclonal plasmacytosis (10% of total cells) and signs of hemophagocytosis, probably due to the underlying severe infectious condition. The patient continued on a prolonged course of antibiotic therapy, showing slow but gradual improvement of both the clinical condition and laboratory test values. This, combined with the improbability that steroids alone could have eliminated all abnormal PC, led to the exclusion of plasma cell leukemia (PCL) suspicion. He was transferred to the cardiac surgery ward, where surgical replacement of the bioprosthetic aortic valve, aortic root, and ascending aorta (Bio-Bentall procedure) was successfully performed. Six months later, after full clinical recovery, blood analyses were repeated showing no evidence of cytopenia or renal failure; MFC on peripheral blood did not detect any monoclonal PC. However, protein electrophoresis revealed the persistence of a single IgM-κ paraprotein (1.3 g/L). Rheumatoid factor (RF) was negative. Six additional months later, follow-up tests confirmed the persistence of a small paraprotein (1 g/L). Given the invasive nature of the procedure, a bone marrow biopsy was deemed unnecessary, but follow-up has been extended to monitor the patient for possible monoclonal gammopathy of undetermined significance (MGUS).

Written informed consent was obtained from the patient, and the procedure was approved by the local ethics committee in accordance with Italian regulations.

The current case report describes an endocarditis mimicking PCL due to the presence of monoclonal circulating PC along with paraprotein, mild anemia, thrombocytopenia and renal impairment. As plasmacytosis in the bone marrow or peripheral blood is mostly a manifestation of plasma cell dyscrasias, clonality assessment to distinguish monoclonal and polyclonal PCs is essential to avoid misdiagnosis. This is particularly important in patients with peripheral circulating PC, as PCL is characterized by an aggressive course where prompt treatment is necessary. While the more recent definition of primary PCL lowered the threshold of circulating monoclonal PC from 20% to 5%[1] detected on the blood smear, the detection of 22% circulating monoclonal PC by MFC in our patient required urgent evaluation. Conversely, reactive plasmacytosis is a transient expansion of plasma cell progenitors and precursors with marked polyclonal peripheral blood plasmacytosis. The mechanism behind polyclonal proliferation of PC is likely multifactorial and is considered a response to other underlying disorders.[2] Several case reports describe reactive plasmacytosis related to hematologic disorders,[3]

infective disorders[4] or autoimmune disorders.[5] Nevertheless, in all these reports, PC are always polyclonal in MFC. Of note, IgM-k paraprotein was also identified. It is unknown whether the patient had a history of MGUS prior to endocarditis. However, since the paraprotein was still positive at the last follow-up, this remains a hypothesis to be considered. It is suggested that autoimmune diseases, infections and inflammatory conditions can stimulate a chronic antigen response with paraprotein production and trigger the development of mutations (e.g., IgH-translocation) and subsequent clonal proliferation.[6] Indeed, several case reports highlight the association between MGUS and infective disorders, including endocarditis,[7] sometimes with long-standing paraprotein detection following infection resolution.[8] Additionally, patients with endocarditis may present IgM RF[9] which can interfere with electrophoresis and serum immunofixation results, even though it was negative in our patient. Although having a prosthetic heart valve is in itself a risk factor for endocarditis,[10] it is also known that patients with MGUS are more susceptible to infectious disorders compared to the general population.[6] A longer follow-up may clarify if the patient really has MGUS. The final aspect to consider is whether the MCF may have produced a false-positive result. The markers CD38$^+$ and CD138$^+$ identify plasma cell populations, but do not distinguish between normal and abnormal PC; although CD56$^+$ is aberrantly expressed in about 75% of myeloma cells and CD56$^-$ is more common in normal plasma cell population, the loss of CD56 is also a hallmark of PCL and poor prognosis in multiple myeloma.[11] To note, the first sample was sent from a spoke center during a period of limited laboratory activity, when only on-call technical support was available. As a result, due to the strong clinical suspicion, no additional markers such as CD117, CD81, or CD27, commonly used in minimal residual disease evaluation to better distinguish benign from malignant PC, were performed. Therefore, evaluation of clonality based on demonstration of altered ratio of cytoplasmic κ

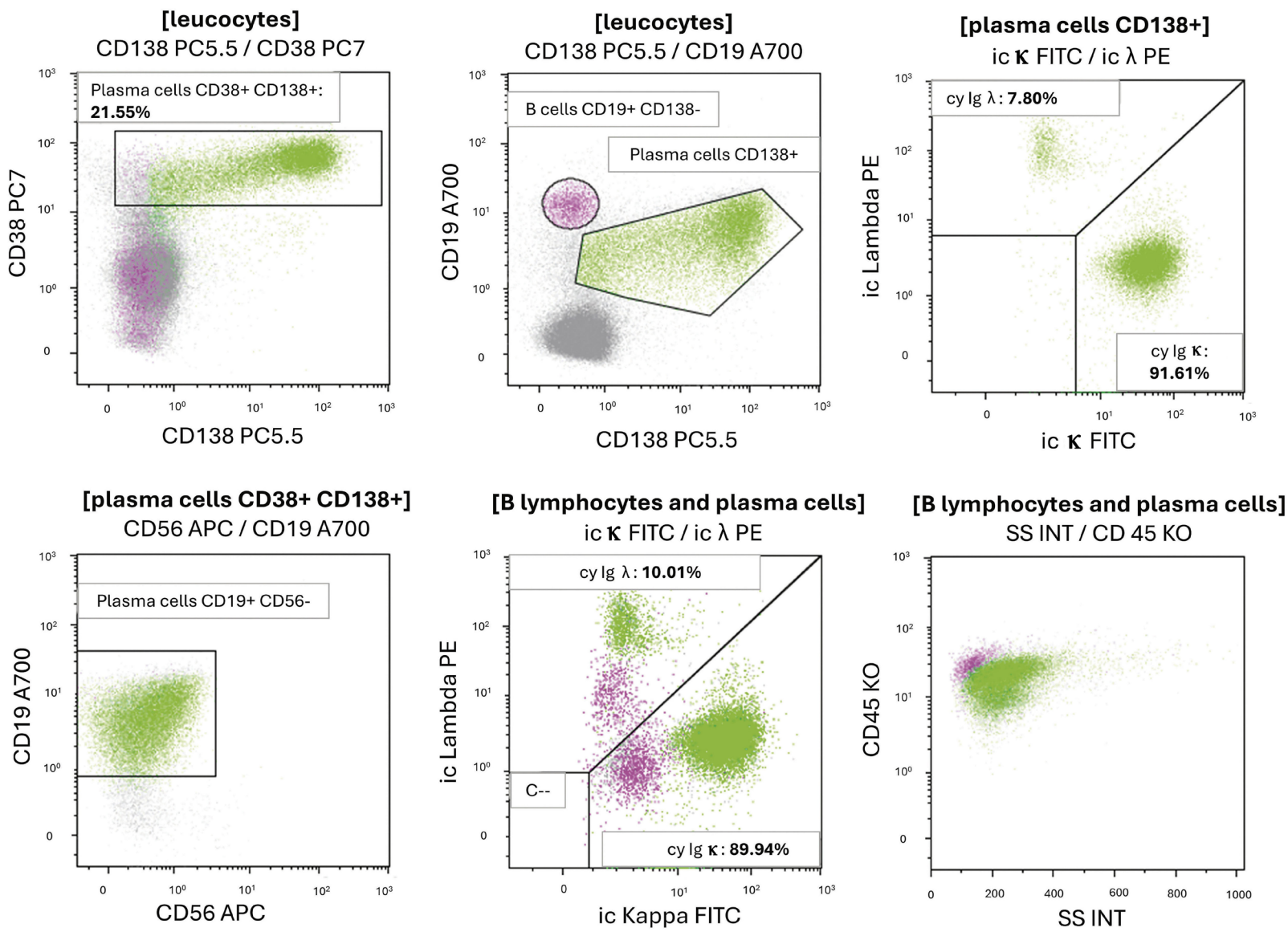

Figure 1. Multiparametric flow cytometric analysis. Plasma cells (PC) represented 21.6% of total leukocytes and were identified based on CD38$^+$/CD138$^+$ expression (top left). PC displayed a CD19$^+$/CD56$^-$ phenotype (top center, bottom left). Intracytoplasmic light chain staining demonstrated κ restriction among CD138$^+$ PC (κ: 91.6%, λ: 7.8%) (top right), while residual B lymphocytes showed a polyclonal pattern (bottom center). On side scatter *versus* CD45 analysis (bottom right), PC showed intermediate to high CD45 expression and low granularity, overlapping with the distribution of polyclonal B cells. The limit of detection and limit of quantification for the assay were 0.02% and 0.05%, respectively, ensuring sensitive and precise identification of plasma cells at low frequencies. ic: intracellular; FITC: fluorescein isothiocyanate; Cy: cytoplasmic; Ig: immunoglobulin; SS: side scatter; INT: intensity; KO: knockout; PE: phycoerythrin.

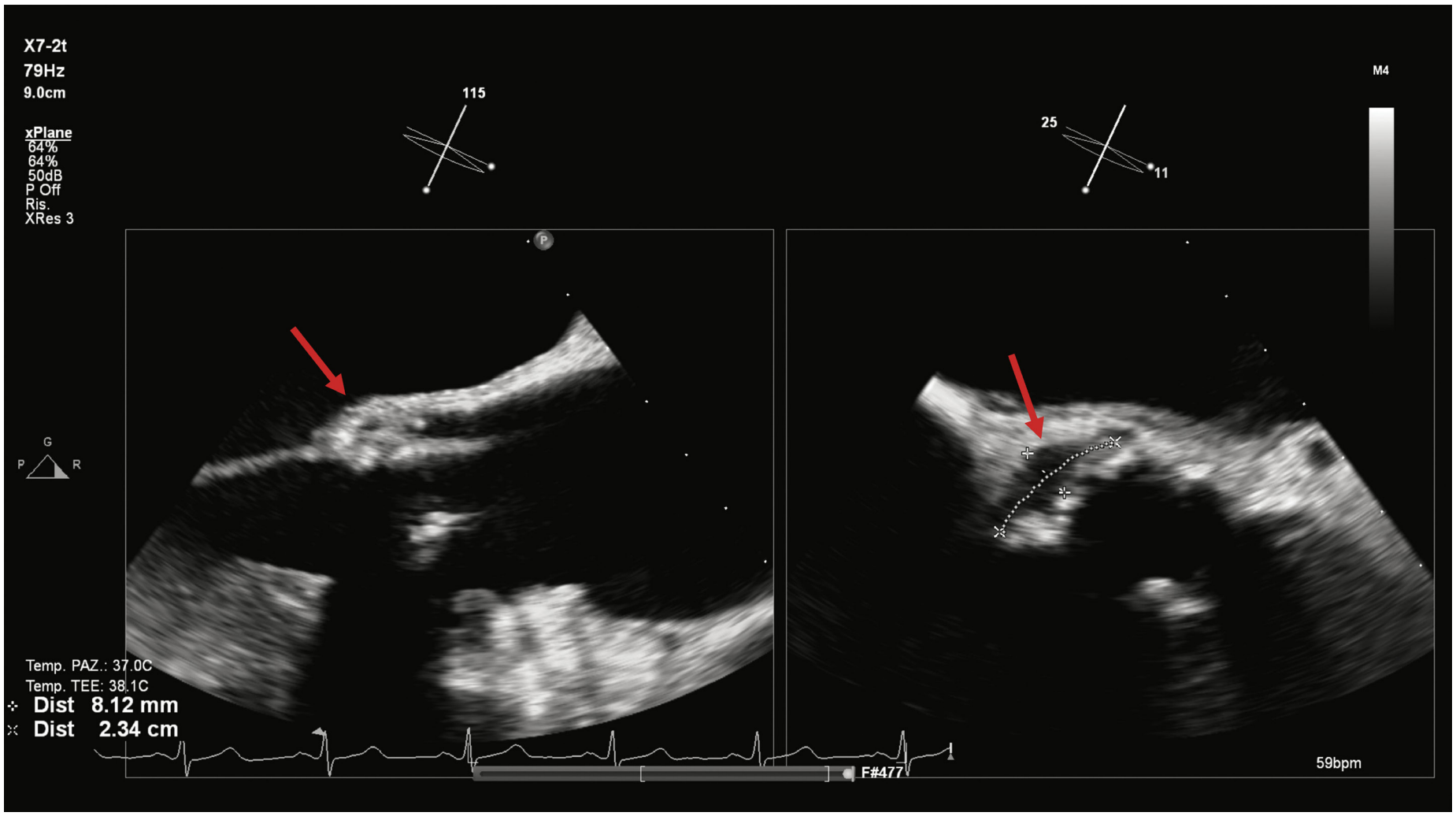

Figure 2. Transesophageal echocardiogram. Transesophageal echocardiogram mid-esophageal view, long axis at 115° and short axis at 25°, focused on the aortic valve, showing the presence of an echo-free, sleeve-like area at the mitral-aortic junction measuring 8x23 mm, suggesting an abscess collection (arrow at the top).

and λ expression is essential. MFC in our patient showed K-restricted PC. It has been reported that monoclonal antibodies can interfere with MFC due to opsonization of B cells, giving both false-positive and false-negative results,[12] as well as non-representative population as seen in hemodiluted samples. However, our patient is naïve, not pre-treated and the sample is from peripheral blood with marked hyperleukocytosis. With the antigenic stimulation related to endocarditis as the initial clue in the quest, we should consider that during the germinal center reaction, antibody diversity is enhanced by the process of somatic hypermutation of the immunoglobulin genes, and clones with high-affinity antibodies are selected for survival. Thus, each germinal center becomes populated by the progeny of only a few B cells. This oligoclonal response might manifest immunophenotypically as slight light chain skewing in germinal center cells in lymph node biopsies.[13] Flow cytometry identifies PC (and generally B cells) as monotypic, meaning they express only one type of light chain. However, while the terms 'monotypic' and 'monoclonal' are often used interchangeably in everyday language, it is important to highlight that monotypic cells are not necessarily monoclonal. Monoclonality can only be confirmed through techniques such as B-cell receptor sequencing, which can determine whether the cells are derived from a single clone.[13] During infections or immune disorders, increased release of paracrine growth factors such as cytokines, IL-6 or IL-10 is known to stimulate plasma cell growth and survival.[14] Therefore, it might be reasonable to think that uncontrolled endocarditis could have caused an overstimulation of PC due to the cytokine storm,[15] shifting transiently the response from oligoclonal to monoclonal. The lack of CD56 expression, which is an adhesion molecule, could have led to the detachment of these PC from the bone marrow and their detection in peripheral blood. Unfortunately, serum cytokines were not investigated, as it is not usual in clinical practice to perform either in plasma cell dyscrasias or in the work-up of infectious disorders; however, the underlying pattern is much more complex and cannot be explained by cytokine levels alone. Furthermore, the endocarditis pathogen remains unknown as blood cultures consistently returned negative and no additional examination was performed of the aortic bioprosthetic valve after surgery.

In conclusion, this is the first reported case of transient peripheral monoclonal plasmacytosis in a patient with endocarditis, whose pathogenic mechanism can only be hypothesized as an extreme exaggeration of a natural response to antigenic stimulation, in a patient with possible pre-existing MGUS. This case underscores the importance of a thorough assessment in patients presenting with overlapping symptoms of infectious and hematological diseases.

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Disclosures

FG has received honoraria from AbbVie, Roche, Takeda, Pfizer, Sanofi, Celgene/Bristol Myers Squibb, Janssen and GlaxoSmithKline; has served on advisory boards for Abbvie, Roche, Takeda, Pfizer, Sanofi, Celgene/Bristol Myers Squibb, Oncopeptides, Janssen and GlaxoSmithKline. BB has received honoraria from Amgen, Janssen, Novartis, BeiGene, Bristol Myers Squibb, GlaxoSmithKline, Jazz Pharmaceuticals, AstraZeneca and Incyte; has served on advisory boards for Amgen and Jazz Pharmaceuticals. All other authors have no conflicts of interest to disclose.

Contributions

GB conceptualized the manuscript, including the development of the primary discussion points. EA, DS and FG oversaw the patient's care and the diagnostics in the ward. GB and FG reviewed him in the outpatient clinic. GB, EA and DS collected laboratory tests and reviewed the medical charts. AD and MG performed and collected echocardiographic images. GAI, SA and GP collected images related to multicolor cytofluorometry. All authors contributed to the writing of the manuscript and brainstorming the discussion. FG and BB supervised the study.

Data-sharing statement

All additional figures, including follow-up flow cytometry and bone marrow trephine biopsy panels, are available upon request from the corresponding author. No other additional data are available due to patient confidentiality.

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