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BRIEF REPORT

Searching for Immunocompromising Conditions in Low-risk Adults After Invasive Pneumococcal Disease: An Opportunity to Uncover Multiple Myeloma Early

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There is a paucity of data on the prevalence of newly diagnosed immunosuppressive conditions following a first invasive pneumococcal infection (IPI) in adults considered to be at low risk for it. A total of 352 IPIs were reviewed over a 7-year period, with 39 (11.1%) ultimately analyzed. A 3.4-year follow-up period revealed that 4 patients (10.3%) had been diagnosed with immunosuppressive conditions. Of these, 3 had been diagnosed with multiple myeloma (MM). These findings indicate that in adults who experience a first IPI and are at low risk for it, MM should be strongly considered and addressed as early as possible.

Keywords. immunodeficiency; immunosuppression; invasive pneumococcal disease; multiple myeloma; *Streptococcus pneumoniae*.

It is unclear whether adult patients without predisposing risk factors require screening for immunodeficiency after first invasive pneumococcal disease (IPD). IPDs remain a prevalent issue in high-risk populations, with the highest incidence observed in patients who have undergone hematopoietic stem cell or solid organ transplantation. Although rare in low-risk subgroups, there is a growing interest in this scenario to prompt investigation into the underlying factors that might have contributed to the occurrence of such infections. Currently, there is no established consensus on when and how to perform this appropriate immunodeficiency screening in patients with a first IPD [1].

Previous studies have shown that immunosuppressive conditions, whether acquired (such as hematologic malignancies, acquired hypogammaglobulinemia, or immunosuppressive medication) or congenital (such as hematologic malignancies), can be detected after IPD [2–4]. However, these studies have either focused on heterogeneous populations or specific immunodeficiency states, which limits the conclusions for a general and efficient approach. Altogether, they have emphasized the need for comprehensive screening strategies to detect underlying immunosuppression that may have predisposed individuals to the IPD. However, there is a lack of studies reporting immunosuppressive states in low-risk populations identified through real-life screening.

The aim of our study is to report the prevalence and types of newly diagnosed immunodeficiencies in a real-world clinical practice in patients with a first IPD who were at low baseline risk of developing an IPD. Additionally, we describe the observed immunodeficiency screening practices and suggest future interventions to optimize the diagnosis of immunosuppressive conditions in this population.

METHODS

We conducted a retrospective cohort study at a tertiary university hospital with 1200 beds, providing medical care to a population of 450 000 individuals. IPD was defined as the isolation of *Streptococcus pneumoniae* in typically sterile samples (blood or other sterile body fluids). All IPD cases between January 2016 and December 2022 were reviewed. This period was selected for review due to the availability of digital medical records. Patients meeting low-risk criteria for IPD were included in the final analysis. These criteria included age >18 and ≤60 years [5], absence of previous pneumococcal vaccination, and the absence of immunocompromising conditions with indication for *Streptococcus pneumoniae* vaccination [6]. Patients with active smoking were included if the pack-year index was <15. A complete basic immunodeficiency screening included HIV screening, serum protein electrophoresis (SPEP) or immunofixation, serum immunoglobulin levels, C3 and C4 levels, lymphocyte subpopulations, and liver/spleen imaging.

Subsequent follow-up was conducted using local electronic medical records and the centralized medical record repository covering all public health care in the Community of Madrid (HORUS Platform). During follow-up, any newly diagnosed immunosuppression, including congenital or acquired

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immunodeficiencies and predefined malignancies, was recorded [6]. The hospital ethics committee approved the study protocol (protocol No. 23/106).

Statistical analyses were performed using SPSS, version 25, for Windows. Categorical variables were assessed using the chi-square or Fisher exact test, as appropriate, while quantitative variables were analyzed using medians and the Kolmogorov-Smirnov test for non–normally distributed data. The diagnostic test's accuracy was evaluated using the MedCalc Software Ltd. Diagnostic Test Evaluation Calculator.

RESULTS

A total of 352 patients with IPD were identified, of whom 313 (88.9%) were not included: 32 (10.2%) were age <18 years, 180 (57.5%) were age >60 years, and 101 (32.3%) had comorbidities that met the exclusion criteria (Supplementary Table 1). Thirty-nine patients were included in the analysis. The median age (interquartile range [IQR]) was 41 (34–48) years. None of the 39 patients had received immunosuppressive or immunomodulatory drugs on admission or in the year before admission (Supplementary Table 2). Pneumonia was the main source of infection in 34 patients (87.2%), and 8 patients (20.5%) required admission into the intensive care unit (Supplementary Table 3). A history of previous severe infection was present only in 1 patient. Concurrent viral coinfection was present in 6 patients (15.4%), all in the group without subsequent immunosuppression diagnosis.

Only 1 patient died during their hospital stay, and there was no confirmation of any immunosuppression. However, the patient had pancytopenia and a high suspicion of a myeloproliferative disorder. Thirty-eight patients were discharged. During a follow-up (IQR) of 3.4 (2.5–4.3) years, 4 patients were diagnosed with immunosuppressive conditions (Table 1). Three of them received a diagnosis of multiple myeloma (MM) 2.7 months, 3.3 months, and 1.1 years after hospital discharge (mean delay, 6.6 months). None of the individuals displayed any significant MM end-organ damage suggestive of MM diagnosis. Specifically, none of them had renal failure, hypercalcemia (serum calcium or corrected calcium for serum albumin), or recorded bone pain in their medical records, and the mean hemoglobin level was 11.0 mg/dL. Additionally, none of them had an SPEP/immunofixation performed during their hospitalization. The fourth patient diagnosed with immunosuppression was a 43-year-old woman who, after 741 days, was diagnosed with stage IV lung adenocarcinoma.

None of the patients received a complete basic immunodeficiency screening. HIV testing and serum immunoglobulin level tests were the most common studies performed (59% and 30.8%, respectively), while spleen imaging and SPEP/immunofixation were the least common (12.8% and 15.4%). During admission, the serum protein gap (SPG), which is the difference

Table 1. Characteristics of Patients Diagnosed as Immune-Compromised After Invasive Pneumococcal Disease

No.	Age, y	Sex	Source of Infection	ICU	Previous Recurrent Infections	Immunosuppression Diagnosis	Delay Until IS Was Made, d	Hb, md/dL	Ig Levels	Complement Levels
1	51	Female	Pneumonia	No	No	Multiple myeloma[a]	82	12.1	↓ IgA and IgM[a]	↓ C3[a]
2	45	Female	Pneumonia	Yes	No	Multiple myeloma[b]	98	10.5	↓ IgA[b]	↓ C4[b]
3	53	Male	Pneumonia	No	No	Multiple myeloma[c]	416	10.6	NA	Unknown
4	43	Female	Pneumonia	No	No	Stage IV lung adenocarcinoma	741	12.3	NA	Unknown

Abbreviations: CH50, 50% hemolytic complement activity of serum; Hb, hemoglobin; ICU, intensive care unit; Ig immunoglobulin; IS, immunosuppression; NA, not available; PET, positron emission tomography.

[a]IgG-Kappa and IgM-Kappa paraproteins; 40% of bone marrow plasma cell infiltration. No bone infiltration on PET scan, serum calcium 8.8 mg/dL, serum albumin 3.6 g/dL, serum creatinine 0.59 mg/dL, IgA 25 mg/dL, IgM 18 mg/dL, IgG 4010 mg/dL, C3 96.40 mg/dL, C4 3.06 mg/dL, CH50 29.05 U/mL.

[b]IgG-Kappa paraprotein; 60% of bone marrow plasma cell infiltration. No bone infiltration on PET scan, serum calcium 9.0 mg/dL, serum albumin 3.0 g/dL, serum creatinine 0.81 mg/dL, IgA 34 mg/dL, IgM 65 mg/dL, IgG 8540 mg/dL, C4 4.03 mg/dL, C3 83.9 mg/dL, no CH50 assessed.

[c]Diagnosed in another institution.

between total protein and albumin (g/dL), was available for 37 (94.9%) patients. It was found to be elevated in the 3 cases who were later diagnosed with MM. In this sample of 37 patients, a cutoff value of SPG > 4.3 showed a sensitivity of 100% (95% CI, 29.2%–100%) and a specificity of 94.1% (95% CI, 80.3%–99.3%) for diagnosing MM (Supplementary Figure 1). The positive predictive value was 60% (95% CI, 28.1%–85.2%), and the negative predictive value was 100% (95% CI, 89.1%–100%).

DISCUSSION

Our study found that multiple myeloma was the most common immunosuppression revealed after a first IPD in adult patients with a low baseline risk for IPD. Basic immunodeficiency screening was incomplete in all patients, indicating a need for improvement. Additionally, SP-GAP demonstrated high sensitivity and specificity as an initial screening tool for MM in this context.

Patients with known hematological malignancies account for 5.7% of IPIs overall, with MM representing the subgroup with the highest incidence and case fatality rate [7]. In line with this, we report with interest a high number of newly diagnosed MM cases in the population selected for our study. The standardized incidence ratio (SIR) of MM, or the number of cases compared with what would be expected, in adult patients over 40 years of age after an episode of community-acquired pneumococcal bacteremia has previously been reported to be 53.5 (95% CI, 21.4–111.4) and 83.2 (95% CI, 22.6–214.8) for pneumococcal meningitis [8]. Although the authors concluded that the absolute risk is low (9 MM cases diagnosed after 405 IPD episodes), we can argue that they included patients regardless of their baseline comorbidities and if they had included only patients without predisposing conditions, the absolute risk would have been much higher, as in our study. MM often leads to increased susceptibility to bacterial infections, which are responsible for 68% of early deaths following diagnosis of MM [9]. IPD is rarely reported as the first sign of underlying MM, although MM is the malignancy with the highest incidence rate of IPD [10]. Seventeen cases of newly diagnosed MM after an IPD were reported between 1978 and 2008 [11]. In contrast to our findings, patients had a higher median age of 65.5 years, with most having renal impairment (67%) and the primary source of IPD being atypical (ie, septic arthritis or pyomyositis).

Our study found a median delay of 6.6 months between IPD and MM diagnosis. A prolonged delay before MM diagnosis is associated with significantly worse disease-free survival and more complications [12]. In addition, Roed et al. reported a 29-fold increase in long-term mortality due to MM after pneumococcal meningitis compared with the general population, and 74% of these MM cases were unknown at the time of IPD [13]. We found that the SPG could have aided in the early diagnosis of MM. Previous studies have reported a lower sensitivity and specificity of the SPG for the diagnosis of monoclonal gammopathy using a cutoff of ≥4.4 (33.7% and 89.2%, respectively) [14]. However, these findings are based on a heterogeneous population and cannot be extrapolated to our study population. Therefore, further studies with larger sample sizes are needed to determine the diagnostic performance in this scenario.

This study has important limitations due to its small sample size and retrospective design. Only 39 patients (11%) of all IPD cases met the low-risk adult criteria, and the small number of immunosuppression diagnoses underpowered our findings to provide a general screening approach recommendation. It is possible that diagnoses made outside of the Community of Madrid public health care system were missed. Moreover, the follow-up period may be insufficient to diagnose MM, smoldering MM, or monoclonal gammopathy of undetermined significance. We did not identify any cases of congenital immunodeficiency, despite previous studies estimating that 22.2% of young adults are newly diagnosed with this condition after experiencing a first IPD, with common variable immunodeficiency (CVI) being the most prevalent [4]. In addition, Cowan et al. reported that 31.6% of patients with an IPD had hypogammaglobulinemia, although some of the patients had previously known underlying comorbidities associated with hypogammaglobulinemia [3]. Only 30.8% (12/39) of our patients had retrievable immunoglobulin levels, and none had a basic immunodeficiency screening. Our screening practices contrast with previously described screening workups where 42.9% of the patients had serum immunoglobulin levels measured and 42% had primary antibody and complement deficiencies screening [3, 4]. This may explain why we did not identify CVI or other humoral deficiency states, except in newly diagnosed MM patients.

One patient was diagnosed with stage IV adenocarcinoma 2 years after IPD. Recent studies have suggested a link between *Streptococcus pneumoniae* and the development and progression of lung cancer [15]. Nevertheless, no previous study has linked IPD to newly diagnosed lung adenocarcinoma, so we cannot draw any conclusions about lung cancer screening in this scenario.

In light of our findings, we suggest that an early search for MM after a first IPD in low-risk adult patients be considered as part of a wider program of immunodeficiency screenings.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. All authors: no reported conflicts of interest.

Transparency declarations. The authors affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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