# An Unexpectedly High IgE Level during Allergic Exploration

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## CASE DESCRIPTION

A 78-year-old man presented to the hospital with hemoptysis. The patient's medical history included active smoking, dyslipidemia, diabetes, and hypertension. A thoracic scan revealed pulmonary emphysema associated with bronchial dilatation and diffuse bronchial thickening. Some calcified micronodules were observed, with a 5.2 mm posterobasal nodule in the right lobe. Based on these findings, a diagnosis of allergic bronchopulmonary aspergillosis (ABPA) was suspected. Laboratory tests revealed an extremely high level of total immunoglobin E (IgE), with a titer of >5000 kU/L [reference value (RV) < 114 kU/L for an adult] and anti-*Aspergillus fumigatus*-specific IgE of 0.2 kU/L (RV < 0.1 kU/L) (Phadia250®, Thermo Fisher). Aspergillus serology was negative and the diagnosis of ABPA was excluded. Complete blood count was normal except for lymphopenia (1.12 × 109/L) and thrombocytopenia (136 × 109/L). Results were also normal for renal and hepatic blood parameters (Cobas®8000, Roche) (Table 1).

Systematic serum protein electrophoresis (SPE) (Capillarys2®, Sebia) found highly suspicious anomalies in the gamma-globulin fraction (Fig. 1A). Given this result, we performed serum immunofixation (IF) (Hydrasys®, Sebia) with 5 antisera [anti-immunoglobin G (IgG), A, M, total kappa, and lambda]. Due to the presence of an isolated lambda monoclonal band, we analyzed anti-immunoglobin D, anti-IgE, and anti-free light chains. IF revealed a wide IgEλ band in addition to a clonal IgGλ band (Fig. 1B-D), estimated at 4.3 g/L and 1 g/L, respectively, on SPE densitometry scan, with barely detectable lambda monoclonal free light chains. Reduction of the sample with betamercaptoethanol led to a more focused ϵ-band that aligned with the lambda band, suggesting monoclonality (Fig. 1D).

We found a low level of serum immunoglobin M at 0.19 g/L (RV: 0.5–1.65 g/L), normal IgG 8.15 g/L (RV: 6.6–13.0 g/L), immunoglobin A 0.76 g/L (RV: 0.75–3.5 g/L), and β2-microglobulin levels 1.72 mg/L (RV: 0.7–1.8 mg/L) by nephelometry (reagents Siemens®, BNII). Ionized calcium was 4.96 mg/dL (1.24 mmol/L) (RV: 4.60–5.09 mg/dL; 1.15–1.27 mmol/L). To investigate the high level of total IgE, dilutions of serum at 1:1000 and 1:5000 revealed consistent IgE concentrations at 1 672 000 kU/L (4.01 g/L) and 1 550 000 kU/L (3.72 g/L), respectively. The presence of interferents (cryoglobulin and immunoglobin M rheumatoid factor) was excluded. Urine immunofixation showed a Bence–Jones protein λ with a total proteinuria of 0.23 g/L (Cobas 8000, TPUC3, Roche) (Fig. 1E).

We measured serum free light chains (sFLC) by nephelometry with Siemens (N-latex FLC, BNII). We found λ sFLC at 1050 mg/L (RV: 8–27 mg/L), κ sFLC at 13.5 mg/L (RV: 7–22 mg/L), and κ/λ ratio at 0.013 (RV: 0.31–1.56). Titers of sFLC were not fully consistent with the IF, showing virtually absent λ sFLC (Fig. 1C). We therefore measured sFLC by turbidimetry with Freelite® (Optilite, Binding Site) with λ sFLC at 246.16 mg/L (RV: 5.7–26.2 mg/L) and κ sFLC at 10.5 mg/L (RV: 3.3–19.4 mg/L). The result of manual dilution of the sample with Freelite excluded prozone/antigen excess (data not shown).

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Bone marrow aspiration identified the presence of 7.5% mature plasmocytes with flaming cytoplasm. Flow cytometry targeted on CD38/CD138 plasmocytes showed that 40% of them expressed CD56, 79% expressed a loss of CD19, and 94% were positive for intracytoplasmic λ light chain (vs 3% for κ light chain). Karyotype analysis and molecular biology showed a *t*(11; 14) *CCND1-IGH* translocation. In the absence of clinical and biological criteria for multiple myeloma (MM), a diagnosis of monoclonal gammopathy of undetermined significance (MGUS) of IgEλ and IgGλ isotype was established and medical follow-up was organized in the clinical hematology ward.

Six months later, repeat SPE and IF displayed the same IgE and IgG bands and total IgE was still >5000 kU/L. λ sFLC was measured at 1380 mg/L and κ sFLC at 12.5 mg/L (N-latex, BNII, Siemens). A second bone marrow aspiration identified 6.5% of mature plasmocytes, 39% expressing CD56, 93.5% expressing a loss of CD19, 9% kappa, and 79% lambda intracytoplasmic light chains.

| QUESTIONS TO CONSIDER |
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| 1. Which diseases can lead to high total IgE levels, excluding allergy? |
| 2. Which biochemical tests should be performed in the presence of a high IgE value? |
| 3. What are the possible interferences with IgE assays? |

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**Table 1. Laboratory results. Urea mg/dL to mmol/L × 0.357; creatinine mg/dL to umol/L × 88.4.**

| Laboratory results | First visit | Second visit | Reference values |
|---|---|---|---|
| Blood counts | | | |
| RBC ($10^{12}$/L) | 4.16 | 4.05 | 4.5–5.8 |
| Hemoglobin (g/dL) | 13.7 | 13.5 | 13–17.5 |
| Hematocrit (%) | 41 | 41 | 40–50 |
| Platelets ($10^9$/L) | 136 | 139 | 150–400 |
| Leukocytes ($10^9$/L) | 6.9 | 5.8 | 4–10 |
| Neutrophils ($10^9$/L) | 5.22 | 4.07 | 1.7–7.5 |
| Eosinophils ($10^9$/L) | 0.19 | 0.26 | (0.7) |
| Lymphocytes ($10^9$/L) | 1.12 | 1.17 | 1.2–4.0 |
| Monocytes ($10^9$/L) | 0.35 | 0.33 | 0.2–1 |
| Biochemistry parameters | | | |
| Proteinemia (g/L) | 70 | 69 | 65–80 |
| Urea (mg/dL) | 39.0 | 30.6 | 15.0–42.0 |
| Creatinine (mg/dL) | 0.83 | 0.76 | 0.67–1.17 |
| IgG (g/L) | 8.15 | 8.21 | 6.6–13.0 |
| IgA (g/L) | 0.76 | 0.84 | 0.75–3.5 |
| IgM (g/L) | 0.19 | 0.20 | 0.50–1.65 |
| IgE (kU/L) | >5000 | >5000 | <114 |
| κ (mg/L) | 13.5 | 12.5 | 7.0–22.0 |
| λ (mg/L) | 1050.0 | 1380.0 | 8.0–27.0 |
| κ/λ ratio | 0.013 | 0.0009 | 0.31–1.56 |
| dFLC (involved FLC-uninvolved FLC) (mg/L) | 1036.5 | 1367.5 | |
| Involved FLC/uninvolved FLC ratio | 77.8 | 110.4 | <100 |
| β2-microglobulin (mg/L) | 1.72 | 1.77 | 0.7–1.8 |
| IgM-rheumatoid factor (U/mL) | <0.4 | 1.2 | <3.5 |
| Serum protein electrophoresis | | | |
| Albumin (g/L) | 42.3 | 41.5 | 40.2–47.6 |
| α1-globulin (g/L) | 2.6 | 2.8 | 2.1–3.5 |
| α2-globulin (g/L) | 6.8 | 6.8 | 5.1–8.5 |
| β1-globulin (g/L) | 3.3 | 3.4 | 3.4–5.2 |
| β2-globulin (g/L) | 2.6 | 2.6 | 2.3–4.7 |
| γ-globulin (g/L) | 9.9 | 10.0 | 8–13.5 |

Abbreviations: RBC, red blood cells; IgA, immunoglobin A; IgM, immunoglobin M; dFLC, difference between involved and uninvolved free light chain.

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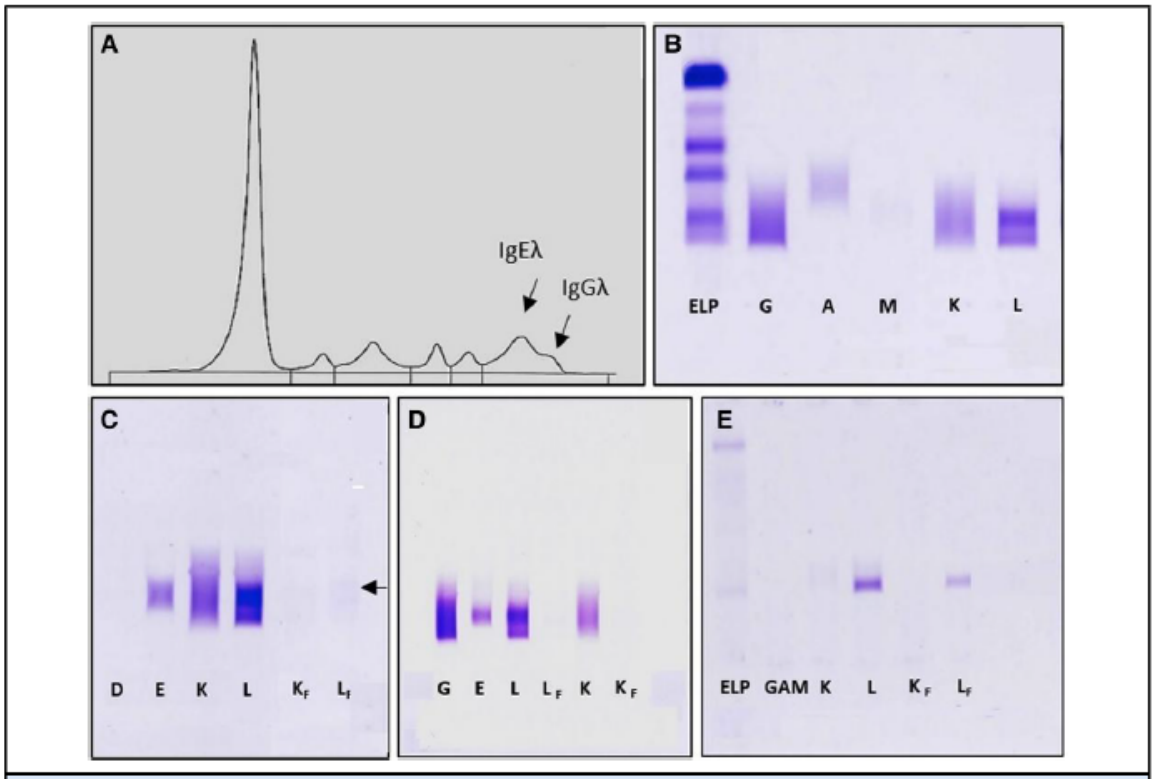


Fig. 1. Electrophoresis and immunofixation. (A), Serum protein electrophoresis (Capyllaris2, Sebia®) first visit. 1: IgEλ, monoclonal. 2: IgGλ, monoclonal. (B), Undiluted serum + 15 µL for each antiserum (Hydragel 9 IF, Sebia) immunofixation first visit. (C), Undiluted serum + 40 µL for each antiserum (Hydragel 1 IF, Sebia) immunofixation first visit. Arrow indicates virtually absent λ sFLC. (D), Undiluted serum + 40 µL for each antiserum (Hydragel 1 IF, Sebia) immunofixation reducted with beta-mercaptoethanol/fluidil (Sebia) first visit. (E), Native urine + 25 µL for each antiserum on urinary immunofixation (Bence–Jones 2/4, Sebia) first visit. Color figure available at https://academic.oup.com/clinchem.

## Final Publication and Comments

The final published version with discussion and comments from the experts will appear in the February 2025 issue of *Clinical Chemistry*. To view the case and comments online, go to https://academic.oup.com/clinchem/issue/71/2 and follow the link to the Clinical Case Study and Commentaries.

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