CORRESPONDENCE

Acquired Osteomalacia Associated with Autoantibodies against PHEX

TO THE EDITOR: Tumor-induced osteomalacia is the most common acquired form of fibroblast growth factor 23 (FGF23)–related hypophosphatemic rickets–osteomalacia (FGF23rHR) and is characterized by excessive secretion of FGF23 from tumors.[1] First-line treatment for tumor-induced osteomalacia is surgical removal of the relevant tumor; however, in 27 to 45% of patients with suspected tumor-induced osteomalacia, such tumors are undetectable despite thorough examination.[2-4] We hypothesized that the absence of a tumor in some patients with suspected tumor-induced osteomalacia might be related to autoantibodies against proteins regulating plasma phosphate levels.

Through a combination of genetic- and tumor-screening approaches, 13 patients with unexplained acquired FGF23rHR were identified; the clinical characteristics of the patients are shown in Tables S1 and S2 in the Supplementary Appendix. Although acquired FGF23rHR affects all races, all the participants in this study were Japanese (Table S3). Serum samples obtained from patients and controls were screened for autoantibodies against causative proteins for congenital FGF23rHR, including DMP1, ENPP1, FGFR1, and PHEX (phosphate-regulating endopeptidase X-linked), with the use of luciferase immunoprecipitation system (LIPS) immunoassays.[5] Immunoassay screening detected autoantibodies against PHEX in 4 of the 13 patients with unexplained acquired FGF23rHR (Patients 9, 11, 12, and 13); none had detectable autoantibodies against DMP1, ENPP1, or FGFR1 (Fig. 1A). These results, obtained with the use of a PHEX–NanoLuc assay (NanoLuc is a luciferase derived from oplophorus gracilirostris, offering higher sensitivity compared with canonical luciferase), were replicated with a construct in which NanoLuc was conjugated to the N-terminal of PHEX (Fig. S1). Serum samples obtained from 18 patients with tumor-induced osteomalacia, 9 patients with X-linked hypophosphatemia, and 10 patients with other endocrine disorders were all seronegative for autoantibodies (Fig. 1A).

Flow cytometry was also used to screen for autoantibodies. Flow cytometry confirmed the presence of autoantibodies in Patients 9, 11, 12, and 13 and identified another patient (Patient 10) with autoantibodies against PHEX. Thus, 5 of 13 patients (38%) had autoantibodies against PHEX (Fig. 1B). This finding suggested that the conformation of the epitope detected in the cell lysate changed from that of the original membranous form in the LIPS assay.

The clinical characteristics of the patients with tumor-induced osteomalacia and of those with X-linked hypophosphatemia are summarized in Tables S4, S5, and S6. Among the 5 patients who were seropositive for PHEX, 1 (Patient 9) had multiple autoimmune findings, including Graves' disease, idiopathic thrombocytopenic purpura,

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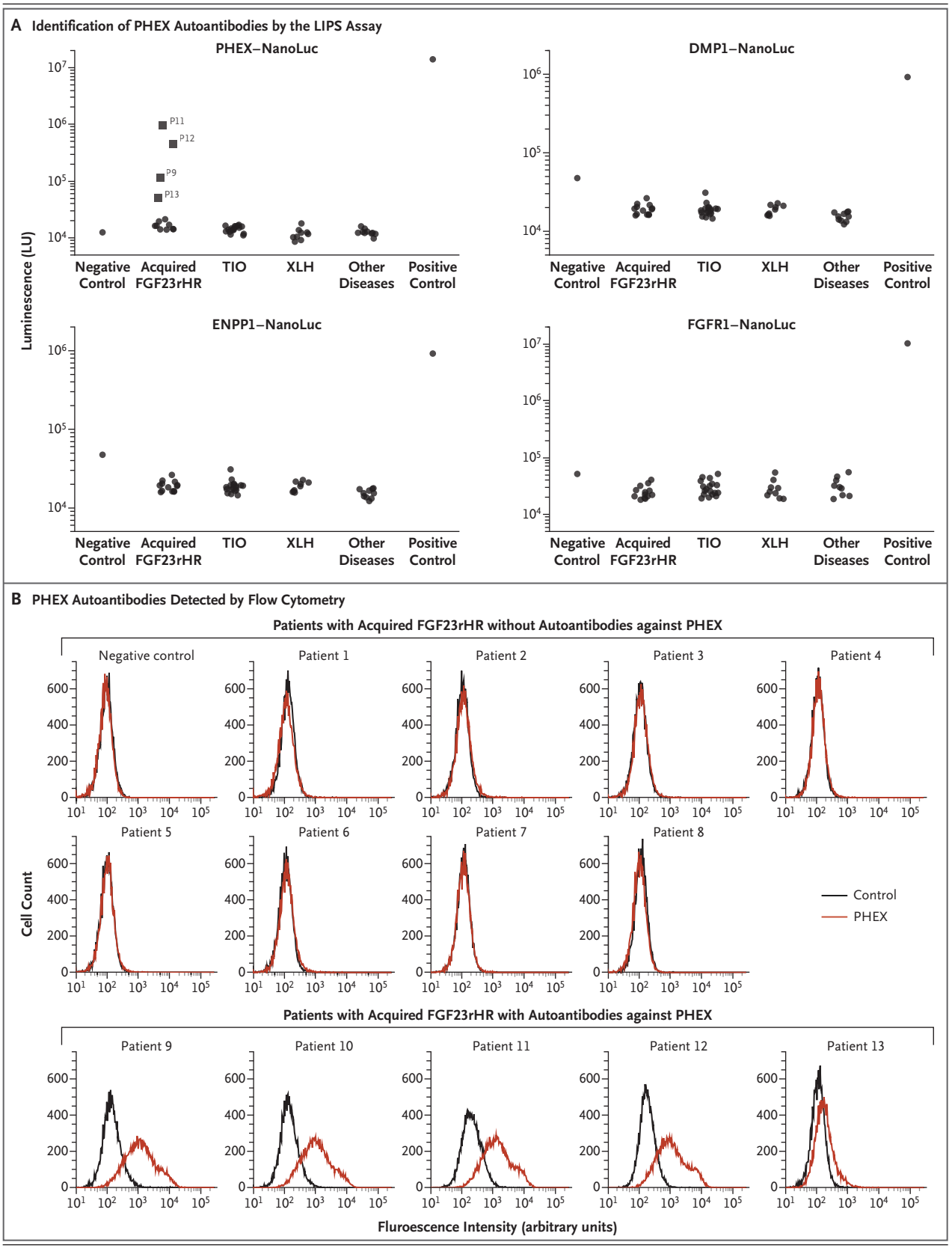

Figure 1 (facing page). Detection of Autoantibodies against PHEX by Means of LIPS Assays and Flow Cytometry.

Panel A shows the results of the luciferase immunoprecipitation system (LIPS) assay for detection of autoantibodies against phosphate-regulating endopeptidase X-linked (PHEX) protein. In the PHEX–NanoLuc construct, PHEX and NanoLuc are fused at the C-terminal of PHEX. A positive control in which commercially available autoantibodies against PHEX were used confirmed the elevated luminescence. LIPS assays were conducted with the use of serum samples from 13 patients with suspected tumor-induced osteomalacia (TIO) without identifiable causative tumors (acquired fibroblast growth factor 23 [FGF23]–related hypophosphatemic rickets–osteomalacia [FGF23rHR] of unknown origin), 18 patients with TIO with identified causative tumors, 9 patients with X-linked hypophosphatemia (XLH), and 10 patients with other endocrine disorders. Among the 13 patients with acquired FGF23rHR of unknown origin, luminescence was elevated in 4 (solid squares in top left plot indicate Patient [P] 11, P12, P9, and P13). For the remaining patients, the luminescence levels were similar to those of the negative controls. Similarly, the results of the LIPS assay targeting autoantibodies against DMP1, ENPP1, and FGFR1 are presented. Elevated luminescence was verified in the positive controls through the use of commercially available antibodies against DMP1, ENPP1, and FGFR1. In all patients, luminescence levels were similar to those of the negative controls, a finding that suggests the absence of autoantibodies against DMP1, ENPP1, and FGFR1 in these patients. LU denotes light units. Panel B shows the results of PHEX autoantibodies detected by flow cytometry. The y axes show the number of human embryonic kidney 293 (HEK293) cells at each level of fluorescence intensity. In Patients 1 through 8, the peaks of fluorescence intensity in the HEK293 cells transfected with an empty vector (control) and in the cells expressing PHEX were identical, which indicates the absence of autoantibodies against PHEX. In contrast, in Patients 9 through 13, peaks of fluorescence intensity were higher in the HEK293 cells expressing PHEX than in the control cells, which indicates the presence of autoantibodies against PHEX.

systemic lupus erythematosus, and antiphospholipid syndrome.

We describe unique cases of autoimmune osteomalacia with pathogenic autoantibodies targeting PHEX. Although further studies are needed to mechanistically determine how PHEX autoantibodies cause osteomalacia, we infer that not only burosumab, an anti-FGF23 monoclonal antibody, but also immunomodulatory therapy might be effective in this subgroup of PHEX-seropositive patients. Our findings also suggest the potential utility of early antibody confirmation to reduce unnecessary tumor-detection procedures and facilitate the prompt initiation of targeted therapies, such as burosumab.

This report documents an acquired osteomalacia associated with autoantibodies against PHEX, which may be termed autoimmune osteomalacia.

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Invasive Strategy for Older Patients with MI

TO THE EDITOR: The results of the SENIOR-RITA (Older Patients with Non–ST-Segment Elevation Myocardial Infarction Randomized Interventional Treatment) trial by Kunadian et al. (Nov. 7 issue)[1] provide compelling evidence that routine coronary angiography and revascularization do not reduce cardiovascular mortality among older patients with non–ST-segment elevation myocardial infarction (NSTEMI). These findings highlight the need to critically assess the role of invasive strategies in this population.

Interestingly, patients who underwent screening but not randomization had clinical and demographic characteristics that were similar to those of the patients who underwent randomization. Among those who did not undergo randomization, 55% received invasive treatment, and 44% received conservative care. These decisions probably reflected careful consideration by treating physicians of factors such as ischemic and bleeding risks, life expectancy, coexisting conditions, indications for noncardiac surgery, quality of life, frailty, cognitive function, patient preferences, and the anticipated risks and benefits of invasive treatment.[2]

We are particularly interested in understanding the priorities that guided these clinical decisions and would appreciate insights from the authors. In addition, we would like to know whether the incidence of cardiovascular events differed between invasive and conservative strategies among the patients who underwent screening but not randomization. Such data could further support personalized treatment as the preferred approach for this vulnerable population.

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2. Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC guidelines for the management of acute coronary syndromes. Eur Heart J 2023;44:3720-826.

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TO THE EDITOR: The SENIOR-RITA trial requires nuanced interpretation in view of the treatment–risk paradox faced by many older patients.[1] Older adults are frequently undertreated for acute coronary syndromes yet are often the most likely to