Primary hyperparathyroidism (PHPT) is a common endocrine disorder known since the 1920s (1); during its near 100 years of history, however, PHPT has proven to be an ever-changing disease. Throughout the developed world, a shift in the presentation of PHPT has happened in the past decades, from cases with severe bone and kidney disease to asymptomatic individuals identified through routine serum calcium screening (2). Indeed, cases with osteitis fibrosa cystica have become a rarity, even in developing countries such as Brazil (3,4), and young endocrinologists in training are sometimes baffled by the gravity of such cases and unsure about their outcome. In parallel with this trend for earlier recognition of PHPT, our understanding of its pathophysiology has also significantly advanced, mainly through the molecular characterization of parathyroid calcium sensing and proliferative pathways, allowing the identification of a genetic predisposition to PHPT (5). In this issue of Archives of Endocrinology and Metabolism, two case reports highlight important nuances of this continuously evolving disorder (6,7).

Oliveira and cols. report a 60 year-old female patient with an orbital brown tumor that significantly regressed after resolution of PHPT (6). Notably, her primary complaint was of facial bone swelling (due to the growth of the brown tumor), while typical PHPT symptoms, such as polyuria, constipation and fatigue, went under-noticed. This is an important reminder of how individual perception of disease manifestations affects its recognition, substantiating how severe cases of PHPT might go unrecognized for some time, even in an era of pre-symptomatic diagnosis. It could be argued that if the diagnosis of PHPT had been made prior to the investigation of the nasal mass, imaging might have sufficed to establish the nature of the bony lesion as a brown tumor and to carefully monitor its evolution, potentially rendering a biopsy dispensable. The most important message of this report, however, is to document the regression of the brown tumor following the resolution of PHPT, a prognostic information that can comfort patients and physicians when dealing with severely symptomatic PHPT.

Considering that in severe PHPT the whole skeleton is under strong PTH stimulus, it is both fascinating and bemusing why brown tumors occur in certain areas. In the case reported by Oliveira, for example, despite all the evident bony involvement (salt and pepper skull, brown tumors), bone mass as assessed by DXA was perhaps disproportionately only mildly reduced (lowest T-score = -2.8 in lumbar spine, information for distal radius is lacking). While this could indicate that the patient had very good peak bone mass to begin with (and this is supported by her substantial bone mass recovery following resolution of PHPT), it might also suggest that specific predisposition to brown tumors exist in certain areas of the skeleton. Surprisingly little is known about local factors or somatic variants rendering a skeletal site more sus-
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PHPT presenting with brown tumors, but with a ge-

netic twist (7). A 62 year-old female patient with bone

pain, fatigue and weight loss was found to have both

PHPT and neurofibromatosis type 1 (NF1), clinically
diagnosed on the basis of café au lait spots and multiple

neurofibromas. An atypical parathyroid adenoma was

identified as the cause of PHPT, and the authors appro-
diately discuss the challenging histopathological dis-
tinction between parathyroid adenoma and carcinoma,

a subject also explored by Oliveira and cols., reminding

us that while severe PHPT cases may be more frequent-

ly associated with parathyroid carcinoma (6,10), pa-

rathyroid adenomas can also present with severe bone
disease.

It may be that the association of PHPT and neuro-

fibromatosis in the case reported by Favere and cols. is

purely coincidental; NF1, however, is no stranger to

the endocrinologist due to its association with pheo-

chromocytoma (11,12). NF1 is caused by mutations in

neurofibromin (encoded by NF1), a negative regulator of

the Ras signaling pathway (13), involved in the pa-

thophysiology of several endocrinopathies and cancer,

thus rendering a hypothetical genetic predisposition to

further endocrine tumors very feasible. Moreover, bony
dysplasia and osteoporosis are hallmarks of NF1, sub-

stantiating a bone environment potentially more prone to lytic lesions in the context of PHPT, as seen in

case. Considering that the advent of massively paral-

lel sequencing techniques are resulting in a paradigm

shift in the identification of predisposition to endocrine

disorders (14,15) and that the analysis of NF1 is well

established in the molecular investigation of pheochro-

mocytoma (16), the association seen in this case should

prompt further work to qualify NF1 to the currently

proposed list of candidate genes for molecular scree-

ning in PHPT (5).

Taken together, these two case reports serve to re-

mind us that severely symptomatic PHPT still exists

and our efforts for early clinical recognition need to

be sustained. They also motivate deeper molecular

exploration of predisposition to PHPT and particular

manifestations such as brown tumors as a means of

identifying mechanisms which might enable earlier case

identification and improved personalized care.

Disclosure: no potential conflict of interest relevant to this article was reported.

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