Title: Early onset effluvium secondary to COVID-19: A clinical and histological characterization

Running head: Early onset effluvium secondary to COVID-19

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To the Editor:

As telogen effluvium (TE) is the most common manifestation of the post-acute COVID-19 syndrome, we read with major interest the publication by Abrantes et al reporting the clinical characteristics of 30 patients with post-COVID acute telogen TE. We would like to commend the authors and bring some other elements to this relevant discussion.

TE is a heterogeneous condition that can be elicited by multiple stimuli. Headington proposed five functional types of TE based on alternations in particular phases of the follicular cycle. Infections are thought to induce TE through the mechanism of immediate anagen release. According to this model, the acute inflammatory state converts follicles from anagen to catagen, leading to the shedding of telogen hairs around 90 days after the infection. Interestingly, the median time for the onset of hair shedding observed by Abrantes et al was 45 days after infection; in the most precocious case, it started 18 days after COVID-19.

This early onset was also observed in two multicentric studies. Moreno-Arrones evaluated 214 cases of acute TE after COVID-19 and noted the onset of hair shedding on an average of 57.1 days after the infection. Starace et al observed an early onset especially when TE was associated with trichodynia. In these cases, the latency from infection to hair shedding occurs at an average of 3 (2–7.5) weeks.

We recently assessed 203 hospitalized patients with confirmed COVID-19, from which 11 (5.4%) reported hair loss with onset early during hospitalization, less than 30 days after the infection. Seven of them were assessed with trichoscopy, trichogram,
and histological evaluation. The detailed information of these cases is presented in supplementary table 1.

Clinically, all cases presented a positive pull test. Trichoscopy did not reveal broken hairs, anisotrichosis, or yellow dots, but it did show some empty follicles. The trichogram from the vertex presented >10% dystrophic anagen hairs (figure 1) and >20% telogen hairs in all cases. Histologically, there is a predominance of anagen terminal follicles, no relevant miniaturization (>10%), and no cases showed more than 25% telogen follicles. No inflammation was evident at the epidermis or throughout the hair follicle (figure 2).

Post-infectious hair shedding has traditionally been classified as an acute TE; however, the hair follicle may respond to infection and inflammation in different ways. A more intense insult could also lead to dystrophic anagen effluvium, which presents as an early onset, as we have demonstrated here. Under COVID-19, the cytokine storm during the inflammatory phase (especially IL6 and TNFα), the severe hypoxia, the oxidative stress, the microthrombotic events and the toxicity of the multiple drugs used for treatment could play a role, especially in the more severe cases. These issues can elicit TE by multiple mechanisms following COVID-19, which can justify different patterns of presentation and time to onset of hair loss.

Further studies exploring the pathogenesis of the early effluvium elicited by COVID-19, as well as its prevalence and possible differences from other acute post-infectious TE, are needed.
References

Figure legends

Figure 1. Early onset effluvium secondary to COVID-19. Dystrophic hair (absence of root sheath and misshaped bulb) on polarized microscopy.
Figure 2. Early onset effluvium secondary to COVID-19. Histopathology: Predominance of anagen follicles, and no inflammation.
**Supplementary table 1.** Demographic data from the seven hospitalized patients with COVID-19 and hair loss.

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