A Letter for Your Doctor

Mast cell involvement in connective tissue conditions, and a gentle first-line conversation

Patient name: ______________________ Date: ______________________

Dear Colleague,

Your patient is working through a patient education course on living with a connective tissue condition such as hypermobile Ehlers-Danlos syndrome or hypermobility spectrum disorder. One section covers the role mast cells appear to play in this population. Your patient wanted to bring that conversation to you directly, with accurate context, rather than arrive with a list of symptoms and no framework. This letter is that context. Every decision below rests with you.

Why mast cells come up in this population

Many people with joint hypermobility also live with two other patterns: orthostatic intolerance, often labeled POTS, and a set of symptoms consistent with mast cell activation. The flushing, the hives, the unexplained reactions to foods or temperature or stress, the gut that flares without a clear cause. The co-occurrence of these three is widely reported clinically and is often described as a triad.

I want to be honest about the state of the evidence. The association is observed often in clinic, yet it is also genuinely debated in the literature. Some recent multicenter work has questioned a clear link between formal mast cell activation syndrome and hypermobility or POTS. So the picture is real enough to take seriously, and unsettled enough to approach as a reasoned trial rather than a fixed diagnosis. That is the spirit in which your patient is raising it.

A note on diagnosis

The diagnostic challenge here is well known. Serum tryptase and 24-hour urinary mediators (such as N-methylhistamine and prostaglandin metabolites) are most informative when drawn during or shortly after a symptomatic flare, and they frequently read normal between episodes. A normal result does not rule the picture out. The consensus diagnostic approach has been widening over recent years, in part through the work of Dr. Lawrence Afrin and colleagues, specifically to catch the many patients who were missed under criteria that required florid lab findings.

What a low-risk first-line trial often looks like

If you find it reasonable, the commonly used first-line approach is conservative and inexpensive, and it doubles as a practical diagnostic trial. A meaningful symptom response can itself be informative. The usual building blocks are these, in your clinical judgment and at doses you consider appropriate:

- An H1 antihistamine, often a non-sedating second-generation agent, sometimes titrated above standard dosing.
- An H2 antihistamine, added alongside the H1, since the combination covers a broader receptor range and often helps gut symptoms.
- A mast cell stabilizer, such as cromolyn sodium or ketotifen, particularly where gastrointestinal symptoms are prominent.
- A leukotriene receptor antagonist, such as montelukast, used by some clinicians as an adjunct when antihistamines alone fall short.
- Trigger awareness, identifying and easing the individual's own provoking exposures, which varies widely from person to person.

The most useful thing I can pass along: how to start, not only what to start

One point I would gently underline above all the rest. Most people in this population are markedly sensitive to medications and supplements alike. The safest path tends to be starting at a very low dose, often a fraction of the usual amount, then increasing slowly over time to find the most effective dose at the smallest quantity. One change at a time, with space between changes so the body can settle.

Here is why it matters so much. A mast cell reads any sudden change as an alert. Even a medication or supplement that will ultimately help a great deal can provoke a reaction when it is introduced too fast or too high. When that happens, the person is reacting to the speed of the change, not to the substance itself, so a genuinely helpful treatment can get abandoned for the wrong reason. Low and slow, one thing at a time, tends to reveal what truly helps.

This letter is patient education context, not medical advice. All clinical decisions rest with the treating physician.

Supportive measures also worth your review

Not all of the support here has to be a prescription. Several over-the-counter supplements are commonly used as wrap-around support in this population, alongside or instead of medication. I am listing the ones that come up most often, purely so they are on your radar. Your review of whether any would be safe and appropriate for this particular patient would be genuinely helpful, given interactions, quality variability, and individual history.

- Quercetin, a plant flavonoid used by many as a gentle, natural mast cell stabilizer.
- Vitamin C, which has a mild antihistamine effect and supports the body's own breakdown of histamine.
- Luteolin, another flavonoid studied for its calming effect on mast cells, sometimes paired with quercetin.
- Diamine oxidase (DAO), the enzyme that clears dietary histamine, taken before meals by those whose symptoms track with food.
- Vitamin D, where levels are low, given its role in immune and mast cell regulation.
- Magnesium, often depleted in this group, and broadly calming to an over-activated nervous system.
- Omega-3 fatty acids, used for general anti-inflammatory support.

The same low and slow principle applies to every item on this page. A supplement is still a change, and the body still reads it as one, so the same care in introducing it gently and one at a time holds true here.

The reason this whole approach is worth considering before more involved workups is simple. It is low in risk, it is reversible, and for the patients who do have mast cell involvement, the relief can be substantial across symptoms that have often been treated in isolation for years.

A clear boundary on my role.
I am a physical therapist, not this patient's prescriber. Nothing here is a directive, a dose recommendation, or a diagnosis. Medications and supplements interact, individual histories matter, and the clinical decision is entirely yours. My only aim is to make the conversation easier.

Thank you for the care you give your patient, and for considering this. I am grateful to be one small part of the team around them.

With respect,

Julie Griffis, PT

Founder, Griffis Sensory-Metabolic Integration
The Pre-PT Course