- **Project Title**: Hymenoptera Venom Allergy in patients with Systemic Mastocytosis: the importance of specific IgE associated with skin tests. The importance of a *multidisciplinary team in the management of patients with systemic mastocytosis.*
- **Name, Country:** Helena Valero Castañer, Spain.
- **Type, duration, and location of Fellowship:** Clinical fellowship, three months duration and in Verona, Italy.
- **Host Institution and Supervisor name:** Azienda Ospedaliera Integrata di Verona, Patrizia Bonadonna.

- **Reports of Clinical Fellowships have to include:**
- **The approximate number of patients observed:** During the external rotation we had medical visits each day from 9 to 13pm and then in the afternoon until 16h with approximately 15-20 patients a day. The approximate number of patients visited during the three months stay would be approximately of 900 patients.
- **The tasks personally developed by the JM and the activities only observed:** During the days that we had the visits with the multidisciplinary team of patients with systemic mastocytosis I did the clinical history and physical examinations, we also performed the skin test both prick and intradermic tests on the patients that had suffered an allergic reaction and did the provocation challenges when appropriate to both food and drugs. The activities only observed during the fellowship were: bone marrow biopsies and aspirates conducted by the hematologist, the skin biopsies on patients with suspected skin mastocytosis performed by the dermatologist and in some days, I was able to observe IV infusions in patients with osteoporosis and bone densitometries.
- **The clinical settings in which he/she was present:** During my external rotation, I had the opportunity to work alongside the multidisciplinary team specializing in mastocytosis. This team included experts from various fields, such as hematologists, dermatologists, and rheumatologists. Collaborating closely with these specialists, I was involved in the initial diagnosis of patients with suspected mastocytosis. This hands-on experience included conducting thorough patient assessments, interpreting diagnostic tests, and participating in the formulation of individualized treatment plans. Moreover, I was able to observe and contribute to the follow-up care of these patients. I witnessed firsthand how ongoing care and interdisciplinary communication are crucial in managing the symptoms and complications associated with this condition. This experience underscored the importance of a cohesive and collaborative approach in providing optimal care for patients with mastocytosis.

  I was also involved in both clinical visits for food and drug allergies. I was actively present in clinical settings where patients underwent drug or food challenges. These challenges are critical in diagnosing allergies and determining safe levels of exposure for patients. I learned about the meticulous preparation and careful monitoring required during food and drug challenges. I observed

how clinicians assess patient history, plan the challenge protocol, and respond to any reaction that might occur during the challenge.

- **The amount of hours spent by week or per day in each department:** In the hematology department I spent about 6 hours a week and in the allergy department about 24 hours a week.

During the rotation, in addition to attending the clinical visits mentioned above, I had the opportunity to collaborate on a project with together with Patrizia Bonadonna who guided us, Massimiliano Bonifacio the reference hematologist and Francesca Norelli, whom with we conducted this project which I will describe below:

In patients reporting a severe systemic reaction (SR) after a Hymenoptera sting, it is essential to make a correct diagnosis of Hymenoptera venom allergy (HVA), perform basal serum tryptase (BST) and further exams in case of suspicion of systemic mastocytosis (SM). HVA is indeed the most common cause of anaphylaxis in patients with clonal mast cell disorders and lifelong immunotherapy with hymenoptera venom is recommended in order to protect the patient of subsequent stings. Current guidelines for HVA diagnosis include an accurate anamnesis, skin tests and dosing serum specific IgE (sIgE) to Hymenoptera venoms. However, sIgE levels in patients with mastocytosis could be particularly low, making the diagnosis more challenging.

The main objectives of our study were to conduct a detailed analysis of demographic, clinical, and laboratory parameters to identify significant differences between patients with HVA and SM and those with HVA without SM. To assess difference in the levels of tIgE and sIgE to Hymenoptera venoms in patients with and without SM and see if there were significant differences between both groups. To emphasize the role of skin tests in diagnosing HVA, especially in patients with SM who may have low sIgE levels, ensuring the correct venom is chosen for immunotherapy.

Our study was a longitudinal observational study involving a cohort of 380 patients: Group A including 97 patients with HVA and a subsequent diagnosis of SM, and Group B including 283 patients with HVA and without SM. Statistical analyses were conducted to identify significant differences between the two groups, focusing on demographic, clinical and laboratory parameters.

For the results: the whole study population was 73% male with a median age of 48 years old at the first SR. A statistically significant difference between the two groups was observed regarding median BST (11.80 µg/L vs 4.50 µg/L, $p < 0.001$) and the severity of initial reaction by Müller grading (3.7 vs 2.7, $p < 0.001$). Moreover, total IgE were significantly lower in Group A (58 kUA/l vs 97 kUA/l, $p=0.005$). Our analysis especially focused on levels of sIgE: as expected, the values were generally lower in Group A, specifically a statistically significant difference was observed in case of sIgE for Vespula spp venom (2.30 kU/l vs 0.90 kUA/l, $p=0.001$) and Polistes dominulus (2.29 vs 1.03 kUA/L, $p=0.025$). In addition, in 5 patients of Group A with undetectable or nearly detectable levels of sIgE, skin tests resulted clearly positive helping the choice of a specific venom to perform immunotherapy.

In conclusion, patients with SM have a greater risk of HVA and more severe SR than the general population. In patients with SM levels of total IgE and sIgE are lower than HVA patients without SM, for this reason skin tests are essential to choose the correct venom for immunotherapy. In suspected cases of SM, in addition to REMA score, low values of sIgE could encourage the clinician to ask for further investigation.

- **Conclusion: conclude with a personal reflection on what you have learned and how you can improve for the future.**

My experience during the rotation has profoundly highlighted the importance of a multidisciplinary team in managing rare and complex pathologies like mastocytosis. Such conditions require a holistic approach that encompasses various medical specialties to ensure the patient receives the most comprehensive and effective care possible. Working alongside hematologists, dermatologists, and rheumatologists, I observed how each specialist's perspective and expertise contribute to a more accurate diagnosis and tailored treatment plan. This collaborative environment not only enhances patient outcomes but also fosters a deeper understanding of the disease from multiple angles, ultimately ensuring that the patient is managed in the best possible way.

The fact of being able to work in a different hospital from mine, learning from other professionals and observing different approaches to patient care has provided me with a broader understanding of medical practices. It has allowed me to compare various methodologies, gaining insights into innovative techniques and best practices that I can incorporate into my future practice, making me a better doctor.

Moreover, reflecting on the study we conducted, I think that this study highlights the significant differences in clinical and laboratory parameters between patients with HVA and SM and those without SM, stressing the critical role of basal serum tryptase (BST), sIgE to hymenoptera venom and skin tests in the diagnosis. Our research demonstrated that patients with SM have lower levels of total IgE and serum-specific IgE (sIgE), could be used together with the REMA score to identify patients at more risk of suffering SM.

	Mastocytosis			
	No	Yes	Total	
	(N=283)	(N=97)	(N=380)	**p-value**
Sex				
1 Male	198 (70.5%)	78 (80.4%)	276 (73.0%)	0.057
0 Female	83 (29.5%)	19 (19.6%)	102 (27.0%)	
#Age	46 (29-57)	50 (44-61)	48 (35-57)	**<0.001**
Grade of index reaction (Mueller)				**<0.001**
I	62 (21.9%)	4 (4.1%)	66 (17.4%)	
II	55 (19.4%)	3 (3.1%)	58 (15.3%)	
III	65 (23.0%)	8 (8.2%)	73 (19.2%)	
IV	101 (35.7%)	82 (84.5%)	183 (48.2%)	
***Basal serum tryptase ug/l**	275, 4.50 (3.30-5.89)	87, 11.80 (8.60-25.10)	362, 5.11 (3.70-8.20)	**<0.001**
***tIgE kUA/l**	283, 97.10 (43.10-260.00)	68, 57.90 (26.40-107.50)	351, 85.00 (40.00-217.00)	**0.005**
***sIgE Ape**	273, 7.20 (0.30-9.00)	90, 1.88 (0.30-9.00)	363, 4.70 (0.30-9.00)	0.121
***sIgE Bombo**	91, 0.90 (0.30-0.90)	49, 0.74 (0.30-0.90)	140, 0.90 (0.30-0.90)	0.084
***sIgE Vespula spp**	283, 2.30 (0.85-7.44)	97, 0.90 (0.45-2.52)	380, 1.62 (0.61-6.22)	**0.001**
***sIgE Vespa crabro**	178, 0.89 (0.30-1.59)	95, 0.59 (0.30-0.90)	373, 0.77 (0.30-1.35)	0.247
***sIgE Polistes dominulus**	281, 2.29 (0.73-9.22)	94, 1.03 (0.42-4.74)	375, 1.81 (0.69-7.97)	**0.025**

#Median, (I-III quartile)
*N, Median(I-III quartile)