Synchronous Systemic Aggressive Mastocytosis and Langerhans Cell Histiocytosis with BRAF p.N486_P490del

André Abdo, MD¹
Jean Francois Emile, PhD²
Philip Bachour, MD¹
Otávio Baiocchi, PhD¹

¹- Lymphoma Center, Hospital Alemão Oswaldo Cruz, São Paulo, Brazil
²- University of Bologne, France
Agenda

- Case presentation (part 1) – ASM
- Case presentation (part 2) - LCH
- Points do discussion
- Conclusion
Case Presentation

52 yof, born in Barretos-SP, married, catholic, G2P2A0
- No comorbidities

In Feb/2018 started to note some ‘little spots’ in the skin, with fast evolution, with pruritus and worsening after exposure to hot water

No other symptoms, and only after 1 year searching almost 10 dermatologists a biopsy was performed, and the diagnosis of Cutaneous Mastocytosis (UP) was done.
Case Presentation

**Diagnosis: Urticaria Pigmentosa**

Courtesy Profa Mirian Soto
Case Presentation

Next 4 months patient got worsening with fatigue, fever, bone pain, weight loss and diarrhea.

She was referred to a Hematologist and after a full investigation Aggressive Systemic Mastocytosis was concluded with involvement of bone marrow (and cytopenias), GI (with diarrhea) , disseminated lytic bone lesions and high tryptase levels.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variante</th>
<th>Medicamentos com potencial beneficio clínico</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIT</td>
<td>D816V</td>
<td>Midostaurin</td>
</tr>
<tr>
<td>TET2</td>
<td>V1395_C1396insL</td>
<td>-</td>
</tr>
<tr>
<td>TET2</td>
<td>c.4044+1&gt;T</td>
<td>-</td>
</tr>
</tbody>
</table>
Case Presentation

- Bone Marrow + cKIT mutation
- Tryptase 90ng/mL
- GI + Diarrhea
- Lytic bone lesions

AGGRESSIVE SYSTEMIC MASTOCYTOSIS

FEB/2020 MIDOSTAURIN 100mg BID
Case Presentation

After 3 months on Midostaurin the patient started to present new skin lesions, including scalp (seborrheic dermatitis), onycholysis and deafness with otorrhea. No one of these new symptoms were due to Midostaurin toxicity and at this point her tryptase levels was 60ng/mL.
Case Presentation

AGGRESSIVE SYSTEMIC MASTOCYTOSIS

OTORRHEA AND DEAFNESS

SCALP DERMATITIS

ONYCHOLYSIS

NEW IDEAS ARE WELCOME !!!
Case Presentation

In Aug/2019 a Video Otoscopy was performed with surgical biopsy and curettage and the soft mass was sent to pathology.
Case Presentation

And the diagnosis was...

*** BRAF V600E/K by PCR was NEGATIVE
Case Presentation

We sent those samples do JFE for review and NGS...

... at this point the patient was extremely symptomatic with absolutely no response to Midostaurin for up to 7 months...

--- and so far we had ... **Aggressive Systemic Mastocytosis AND Langerhans Cell Histiocytosis**

In Nov/2020 after discussion with patient and Family, we started Cladribine 0.14mg/kg D1-D5 for 6 cycles.
SYSTEMIC MASTOCYTOSIS (SM) AND ASSOCIATED MALIGNANT BONE MARROW HISTIOCYTOSIS – A HITHERTO UNDESCRIBED FORM OF SM-AHNMD

ZBIGNIEW RUDZKI¹, KARL SOTLAR², ANDRZEJ KUDELA³, JOLANTA STARZAK-GWOŹDŹ³, HANS-PETER HORNY⁴
Case Presentation

Prof JFE review and NGS... (ear soft tissue)

Conclusion:

Altération(s) génétique(s) détectée(s):

**BRAF** mutation de type: c.1457_1471del, p.(486_490del), VAF*: 38.2%,

Séquences de référence **BRAF**: NM_004333.4

Langerhans Cell Histiocytosis with **BRAF** c.1457_1471del

Courtesy Prof JFE
Case Presentation

After 6 cycles of Cladribine...

Tryptase <20ng/mL (normal range)
Improvement UP
No more diarrhea
BUT

Bone Marrow Biopsy

CD1a

S100

Ki-67

CD117

Author's collection
Case presentation – May/2021

Aggressive Systemic Mastocytosis in CR Mulsisystemic Langerhans Cell Histiocytosis Refractory

Langerhans cell histiocytosis with *BRAF* p.N486_P490del or *MAP2K1* p.K57_G61del treated by the MEK inhibitor trametinib

Yoav H. Messinger¹ ☞ | Bruce C. Bostrom¹ ☞ | Damon R. Olson² | Nathan P. Gossai¹ | Lane H. Miller¹ ☞ | Michael K. Richards¹
Case presentation

In June/2021 we started Trametinib 1mg daily

1 month after: No more fatigue, No more dermatitis, Recovery almost all hearing, No more bone pain... Went to GYM...
- Keep no sign (clinical and tryptase) of Mastocytosis

Have developed grade 2 acneiform eruption on face (good response to topical steroids)
Last follow up ... Sep/2021

3 months Trametinib

15 days after Pfizer
Last follow up ... Oct/2021
Some points to discussion, more doubts

- this is the first (in our knowledge) case with Synchronous ASM and MS-LCH

- ASM : TET-2 and KIT mut + MS-LCH : BRAF non V600E/K mut

- Are they spectrum from a common myeloid progenitor?

- Is MS-LCH in this case a SM-AHNMD?
Conclusions

- Rare presentation on rare diseases... We need to share datas

- and Probably BEM (Clinical trial) would be replace for precision medicine

- Genomic/molecular information was the turning point in this case

- Partnership is indisputably important for low income countries
Thank you

Special thanks to:
CGP (the patient) and her Family
Jessi and Kathy (ECDGA)