CONVEGNO FISiM

Firenze, CSF Montedomini - “Il Fuligno”

24-25 ottobre 2024

MDS and autoimmunity

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Myelodysplastic neoplasms and autoimmune phenomena –
FISiM group

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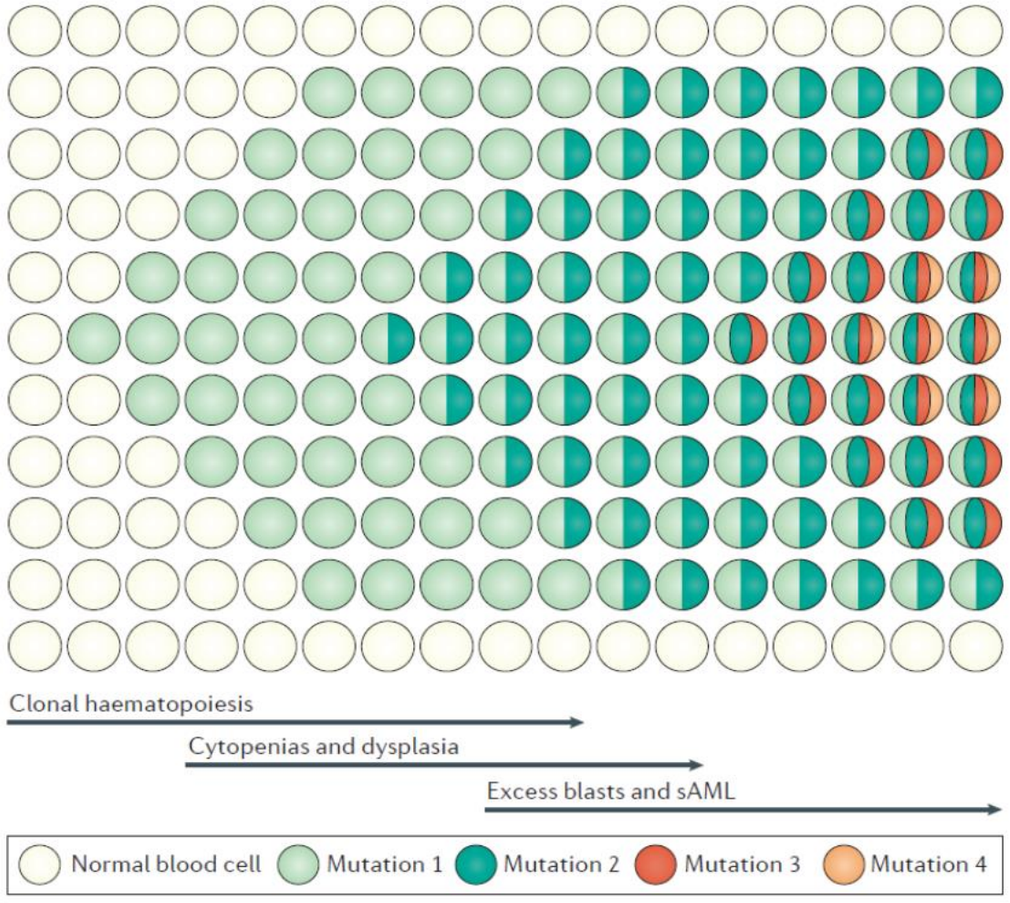
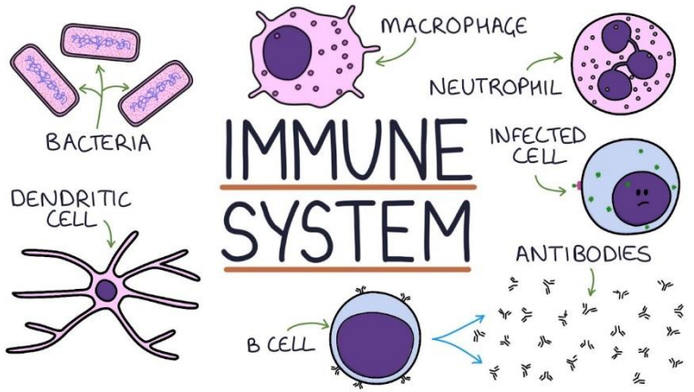
Myelodysplastic syndromes and autoimmune phenomena

MDS Pathogenesis

- Clonal disease of the hematopoietic stem cell that accumulates genetic lesions (molecular lesions and chromosomal abnormalities >70% of cases)
- Mainly of epigenetics (methylation, histone acetylation, splicing, etc.).





In this process the Immune system is not an innocent spectator!

Sperling et al. Nature Reviews Cancer 2017

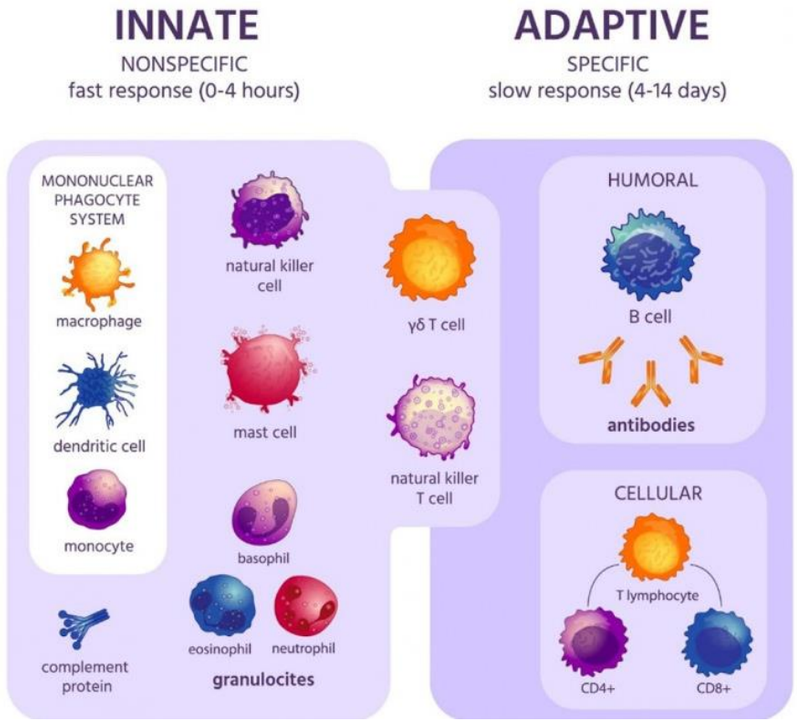
Myelodysplastic syndromes and autoimmune phenomena

Low risk MDS → ineffective erythropoiesis → peripheral cytopenia → Median OS 8 -10 years

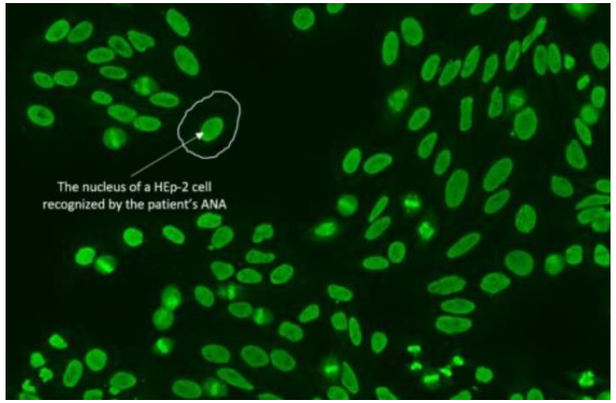
→ **The production of autoantibodies against BM precursors and peripheral blood cells may further impairs myelopoiesis**
→ **The production of proapoptotic/pro-inflammatory cytokines favour ineffective hemopoiesis**

High risk MDS→ blast proliferation and **leukemic evolution →** Median OS 6 months – 2 years

→ **The immune niche becomes tumor supportive and favors leukemic escape**
→ **A switch from pro-apoptotic to tumor-permissive immune system is observed**

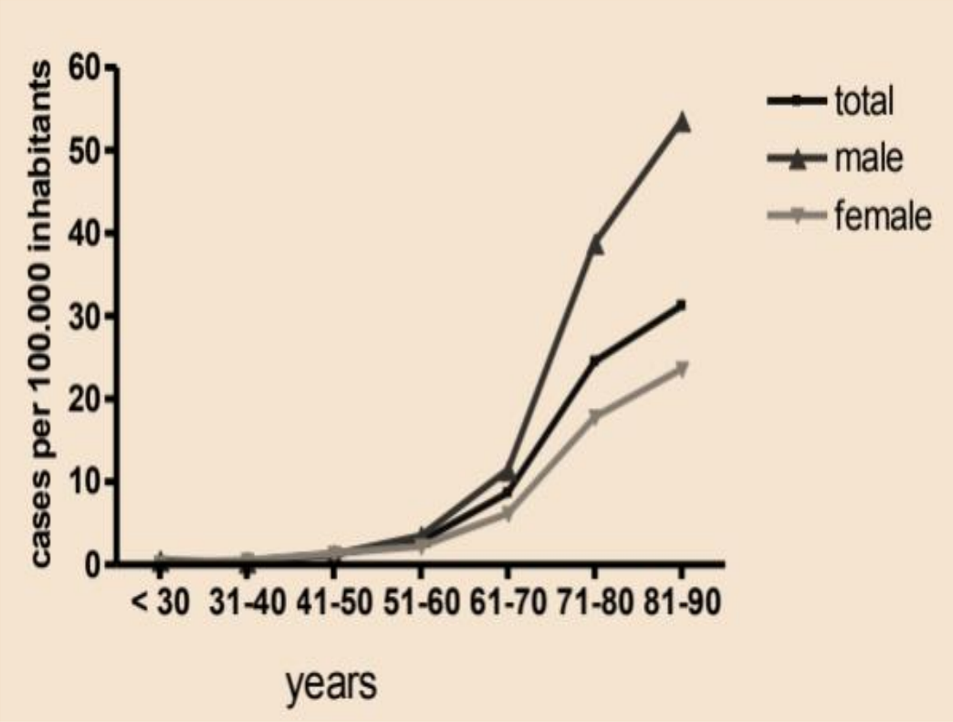


As in MDS, the incidence of autoimmune phenomena increases with age as the physiological attempt to eliminate senescent cells/structures



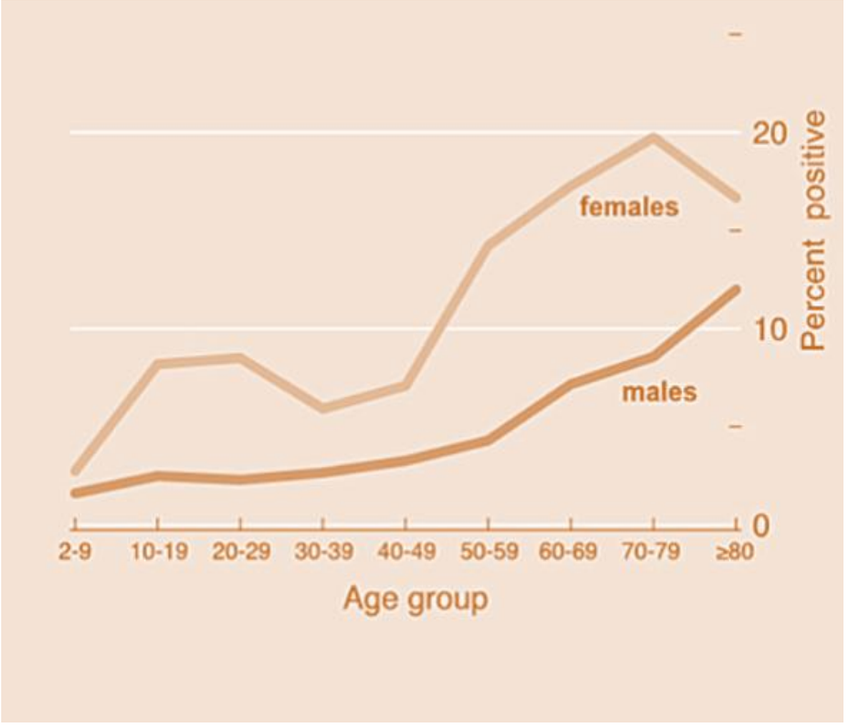
MDS

- Incidence of 4/100,000 people year, increasing with age
- Median age 70 years (<10% <50 years)
- M>F



AIDs

- Incidence of 4000/100,000 people year
- % of ANA positivities increases with age
- F>M



ICUS…IDUS…MDS and autoimmunity

EXPERT REVIEW OF HEMATOLOGY, 2017
https://doi.org/10.1080/17474086.2017.1339597

REVIEW

The relationship between idiopathic cytopenias/dysplasias of uncertain significance (ICUS/IDUS) and autoimmunity

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ABSTRACT

Introduction: This review examines the several lines of evidence that support the relationshi
myelodysplasia and autoimmunity, i.e. their epidemiologic association, the existence o
immune-mediated physiopathologic mechanisms, and the response to similar immunos
therapies. The same relationship is reviewed here considering idiopathic cytopenia of unc
nificance (ICUS) and idiopathic dysplasia of uncertain significance (IDUS), two recently
provisional conditions characterized by isolated/unexplained cytopenia and/or dysplasia
bone marrow cells.

Areas covered: The review focuses on alterations of cytokine profiles, telomere/telomerase a
receptors, and on increased myelosuppressive mediators and apoptotic markers in both myel
and autoimmunity. In addition, the presence of an autoimmune reaction directed again
precursors is described in refractory/relapsing autoimmune cytopenias (autoimmune hemoly
immune thrombocytopenia, chronic idiopathic neutropenia), possibly contributing to their e
ICUS/IDUS/bone marrow failure syndromes.

Expert commentary: The increasing availability of omics methods has fuelled the discuss
role of somatic mutations in the pathogenesis of IDUS/ICUS, clonal hematopoiesis of ind
potential, and clonal cytopenias of undetermined significance, and in their possible evolu
more attracting is the involvement of the genetic background/accumulating somatic m
cytopenias with autoimmune alterations.

- The relationship between MDS and autoimmunity is supported by
  - **epidemiologic association**
  - **response to similar immunosuppressive therapies**
  - **common immune-mediated physiopathologic mechanisms**

- Several mechanisms are involved:
  - **alterations of cytokine profiles**
  - **telomere/telomerase and toll-like receptors**
  - **increased myelosuppressive mediators and apoptotic markers**
  - **presence of an autoimmune reaction directed against marrow precursors in refractory/relapsing autoimmune cytopenias (ITP, AIHA, CIN) that may contribute to their evolution to ICUS/IDUS/BMF**

Immune phenomena in myeloid neoplasms include autoimmune cytopenias/diseases and immunodeficiency

Autoimmunity reflects a **dysregulated immune tolerance and surveillance** and may result, along with contributing environmental and genetic factors, in an increased incidence of both tumors and infections.

TABLE 1 | Main evidences of immune system involvement in myeloid neoplasms.

Epidemiological associations with autoimmunity	- MDS is associated with systemic and organ specific disorders, such as RA, SLE, vasculitis, thyroid autoimmune diseases, SS, AIHA, ITP, PRCA, and immune-mediated hemostatic disorders in about 20% of cases. - CMML are complicated in up to 30% by vasculitis and ITP. - MPN and AML are occasionally complicated by autoimmune cytopenias and diseases.

- **MDS and chronic myelomonocytic leukemia (CMML)** are complicated in **up to 20- 30% by vasculitis subtypes**, more commonly Behçet's-like syndrome, relapsing polychondritis, polyarteritis nodosa and giant-cell arteritis.
- **CMML is also frequently complicated by ITP** either concomitant or preceding its diagnosis, while **AIHA and PRCA are occasionally observed**.

- Case-reports/small series of immune-mediated hemostatic disorders have been described in MDS, CMML, MPN, and AML. These included **acquired hemophilia A, thrombotic thrombocytopenic purpure, and anti-phospholipid syndrome**, that may be life-threatening.

Barcellini et al Front Immunol 2021

Low-Risk Myelodysplastic Syndrome Revisited: Morphological, Autoimmune, and Molecular Features as Predictors of Outcome in a Single Center Experience

Bruno Fattizzo[1,2], Giorgia Virginia Levati[2], Juri Alessandro Giannotta[1], Giulio Cassanello[2], Lilla Marcella Cro[3], Anna Zaninoni[1], Marzia Barbieri[3], Giorgio Alberto Croci[4], Nicoletta Revelli[5] and Wilma Barcellini[1]*

Among **157 patients** at least one **positivity** was observed in about half of the patients (**46%**):

- **DAT positivity in 21.5% (51 tested),**
- **anti-PLT in 52% (38 tested),**
- **anti-erythroblasts in 67% (88 tested).**

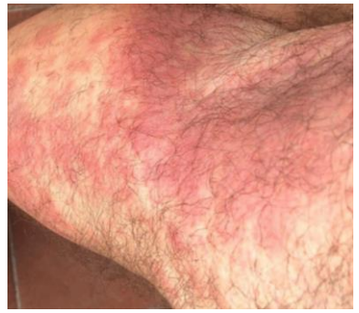
These **"autoimmune-MDS" patients** were **younger (p=0.001)**, were predominantly **female (p=0.01)**, were more frequently **thrombocytopenic** (PLT <100 x10^9/L 38% versus 17%, p=0.02), and more often displayed **hypocellular bone marrow** (19% versus 9%, p<0.01).

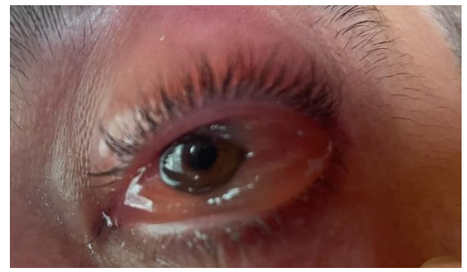
Patients with anti-erythroblast autoantibodies showed **lower Hb levels, higher LDH values, and hypocellular marrow** (18% versus 6%)
And displayed reduced T-helper 1 (IFN-γ, TNF-α) and increased T-helper 2/17 profile (IL-6, IL-17, TGF-β)

	Positive	Negative
Anti-erythroblast antibodies (ng/mL)	727 ± 136	118 ± 17
IFN-gamma (pg/mL)	1,095 ± 146	1,169 ± 54
TNF-alpha (pg/mL)	125 ± 33	275 ± 107
IL-10 (pg/mL)	647 ± 158	886 ± 344
IL-6 (pg/mL)	71 ± 3	65 ± 4
IL-17 (pg/mL)	326 ± 122	120 ± 99
TGF-beta (pg/mL)	12,666 ± 1,298	10,870 ± 1,939

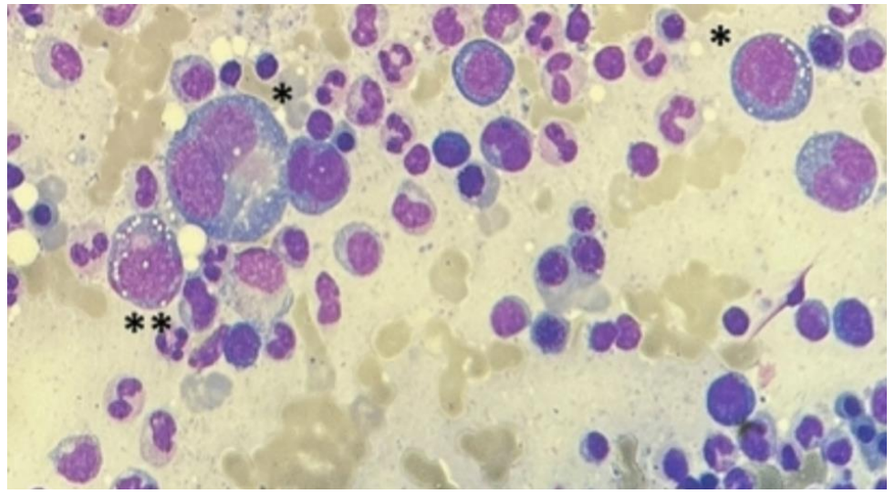
VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome

Beck DB, et al. N Engl J Med. 2020;383(27):2628–2638.





- is caused by **UBA1 somatic mutations** and is characterized by **late-onset systemic autoimmune inflammation and blood abnormalities such as cytopenia**, vacuolation of myeloid/erythroblastic cells, and myelodysplastic syndrome (MDS).



- The clinical picture may be **extremely heterogenous**, **mimicking different other systemic rheumatologic entities**

Diagnosis should be **strongly considered**: adult patient with an **unexplained systemic inflammatory condition** (fevers, neutrophilic dermatosis, relapsing polychondritis, ocular inflammation and other systemic inflammatory symptoms) **accompanying MDS or cytopenias.**

- Treatment with steroids effective but limited by toxicity.
- In a French experience azacitidine was effective in 5/11 patients with VEXAS/MDS (46%) *Comont T et al, BJH 2022*

PNH: an intriguing story…

Leukemia
https://doi.org/10.1038/s41375-021-01190-9

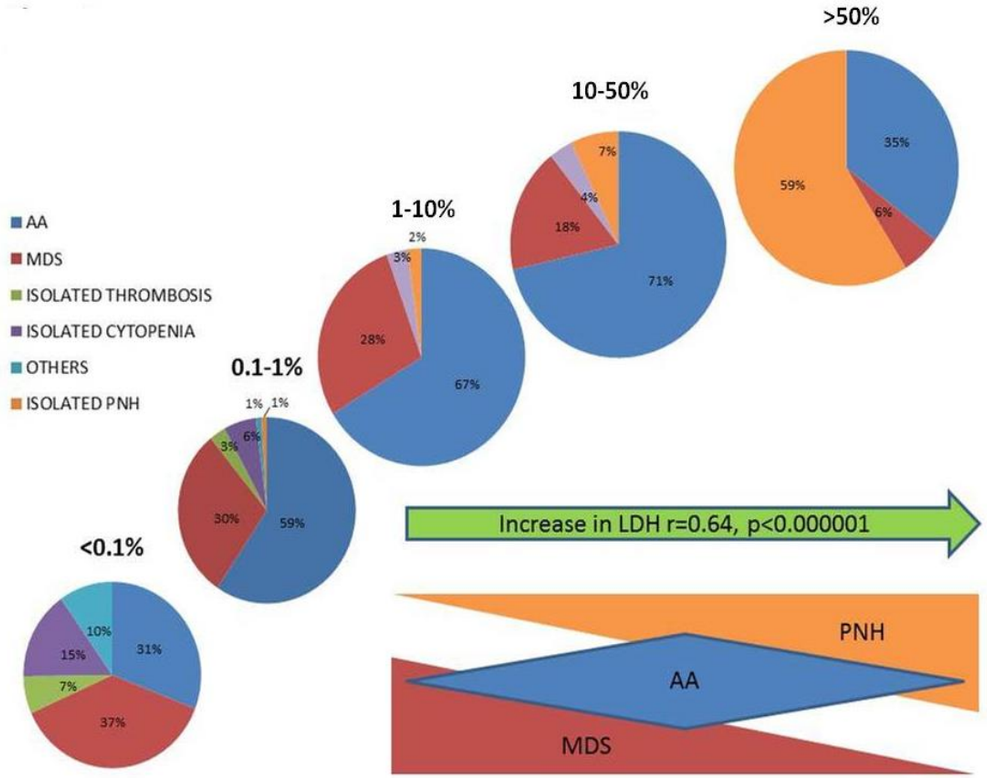
ARTICLE

Myelodysplastic syndrome

Clinical and prognostic significance of small paroxysmal nocturnal hemoglobinuria clones in myelodysplastic syndrome and aplastic anemia

Bruno Fattizzo[1,2,3] · Robin Ireland[1] · Alan Dunlop[1] · Deborah Yallop[1] · Shireen Kassam[1] · Joanna Large[1] · Shreyans Gandhi[1] · Petra Muus[1] · Charles Manogaran[1] · Katy Sanchez[1] · Dario Consonni[2] · Wilma Barcellini[2] · Ghulam J. Mufti[1,4] · Judith C. W. Marsh[1,4] · Austin G. Kulasekararaj[1,4]

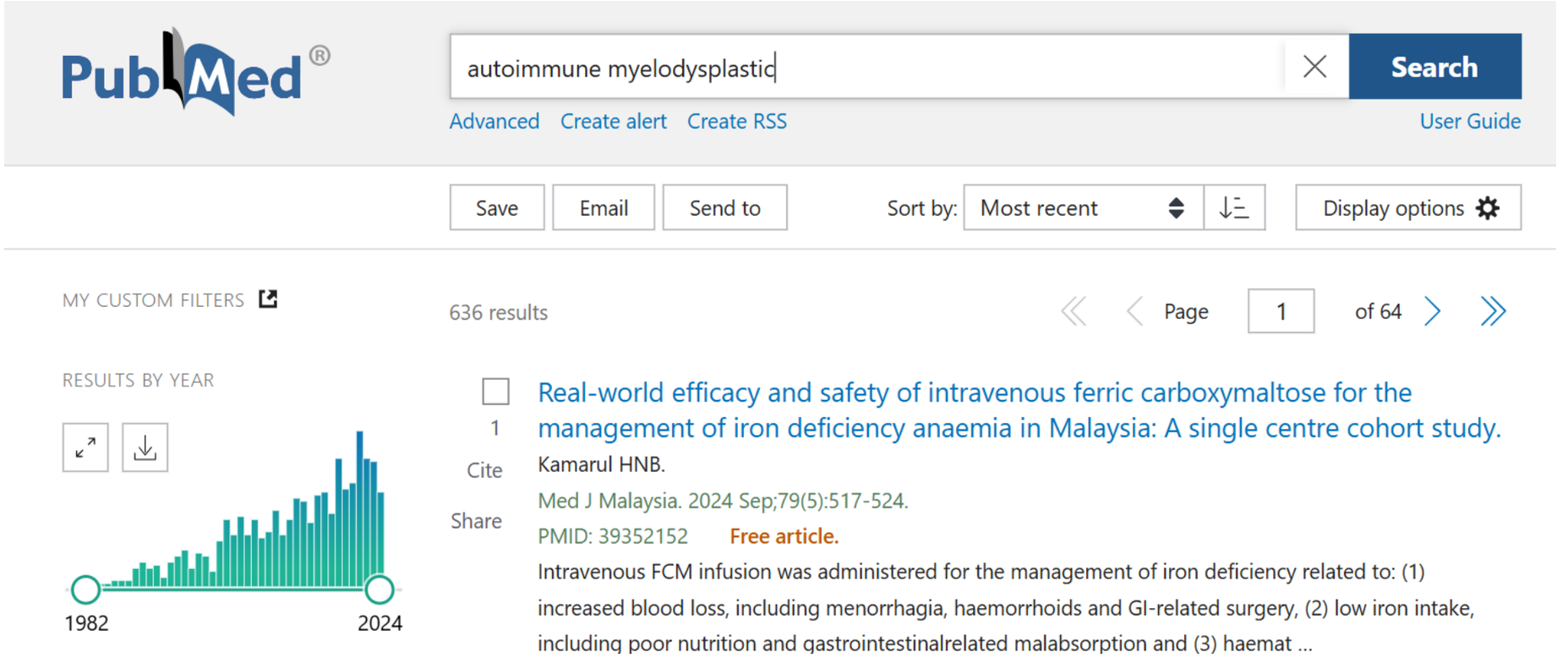
PNH clones in 3085 patients with cytopenia



- classical PNH with large clones (>50%)
- AA cases mainly medium clones (10-50%)
- MDS cases mostly presented with small (<10%) and very small clones (<1%)
- LDH significantly augmented along with clone size increase
- Thrombotic complications were more frequent in patients with larger clones (7 to 21%, p<0.0001)

- PNH positivity correlates with better response to IST and HSCT in MDS and AA,
- The presence of at least 0.01% PNH clone correlated with better survival

Is there room for further studies?



On pubmed:

- «autoimmune and mds» → 636 results, mostly case reports, 109 in the last 10 years
- «immunosuppressive and mds»→ 745 results in the last 10 years, mostly case reports
- No specific guidelines

Gruppo di lavoro FISIM: MDS e autoimmunità

Da metà giugno 2024 sono state raccolte le proposte dei Centri tramite un doodle Google Moduli

L’8 luglio 2024 abbiamo svolto una riunione online a cui hanno partecipato 18 Ematologi da tutta Italia

La proposta emersa è stata quella di uno studio retrospettivo/prospettico:

Marcatori e fenomeni autoimmuni nei pazienti con neoplasie mielodisplastiche: uno studio multicentrico retrospettivo/prospettico

Modalità di reclutamento e procedure dello studio:

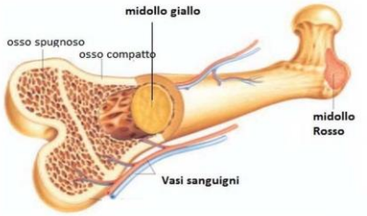
1. inclusione nello studio dei pazienti già inseriti in registro FISIM
2. registrazione dello studio come "sotto-studio« nell’ambito del registro FISIM
3. preparazione di una lista di «record» da includere nella CRF del Registro FISIM per registrare i fenomeni autoimmuni e le terapie eseguite per tali fenomeni
4. invio dell’alert ai centri per iniziare a inserire i dati

CRF «autoimmune»

Diagnosi

1. Indici di emolisi: LDH, Ret, bilirubin tot/indir, haptoglobin
2. C3, C4, PNH clone neut/mono/eritro
3. ANA, ENA, anti-DNA, ASMA, AMA, Anti CCP, FR
4. LAC, ACA, anti-Beta2 gp1
5. Coombs diretto e indiretto
6. Anti-PLT
7. Anticorpi anti-neutrofili
8. Ipocellularità midollare/PRCA/aplasia MGK o Granulo
9. Infiltrato LGL su midollo si/no, %, TCR clonale?
10. NGS mieloide
11. Clinical features (testo libero)
12. Comorbidità autoimmuni note (testo libero)

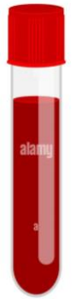
PB labs



BM labs

S&S

CRF «autoimmune»

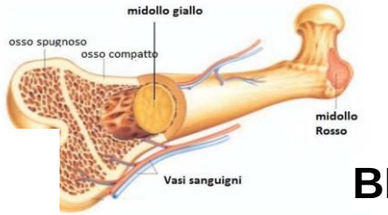


PB labs

Follow up

Indici di emolisi: LDH, Ret, bilirubin tot/indir, haptoglobin

1. C3, C4
2. PNH clone neut/mono/eritro
3. Ipocellularità midollare/PRCA/aplasia MGK o Granulo
4. Infiltrato LGL su midollo si/no, %, TCR clonale?
5. NGS mieloide
6. Clinical features (testo libero)
7. Comorbidità autoimmuni note (testo libero)



BM labs

S&S

CRF «autoimmune»

Terapia

Steroide
- **Reason to treat:** anemia/piastrinopenia
- tipo: prednisone/metilprednisolone/desametasone
- **dose e posologia (testo libero)**
- **Data inizio e data fine**
- **risposta sec IWG / AEs**

Ciclosporina
- Reason to treat: anemia/piastrinopenia
- dose e posologia (testo libero)
- Data inizio e data fine
- risposta sec IWG / AEs

MTX
- Reason to treat: anemia/piastrinopenia
- dose e posologia (testo libero)
- Data inizio e data fine
- risposta sec IWG / AEs

ATG
- Reason to treat: anemia/piastrinopenia
- dose e posologia (testo libero)
- Data inizio e data fine
- risposta sec IWG / AEs

Androgeno
- Reason to treat: anemia/piastrinopenia
- Tipo (testo libero)
- dose e posologia (testo libero)
- Data inizio e data fine
- risposta sec IWG / AEs

Altro: specificare
- Reason to treat: anemia/piastrinopenia
- dose e posologia (testo libero)
- Data inizio e data fine
- risposta sec IWG / AEs

Prospettive

- Caratterizzare i fenomeni autoimmuni di laboratorio e clinici nei pazienti MDS inclusi nel registro Italiano
- Valutare le terapie somministrate con attività immunomodulante/anti-infiammatoria e il relativo outcome --> inclusi gli eventi avversi
- Valutare l'impatto dei fenomeni autoimmuni sulla severità (necessità trasfusionali) e sull'outcome dell'MDS (evoluzione leucemica e sopravvivenza)
- Inclusione della VEXAS syndrome???
- **Chi, quando e come trattare con la terapia immunosoppressiva?**
- **Lavoro preliminare potrebbe essere una «Consensus» con Delphi panel sulla tematica.**

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Grazie per l'attenzione!