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# Chronic neutrophilic leukaemia and plasma cell-related neutrophilic leukaemoid reactions

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Chronic neutrophilic leukaemia and plasma cell-related neutrophilic leukaemoid reactions

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**Summary**

Many cases reported as 'chronic neutrophilic leukaemia' have had an associated plasma cell neoplasm. Recent evidence suggests that the great majority of such cases represent a neutrophilic leukaemoid reaction to the underlying multiple myeloma or monoclonal gammopathy of undetermined significance. We have analysed all accessible reported cases to clarify the likely diagnosis and to ascertain whether toxic granulation, Döhle bodies and an increased neutrophil alkaline phosphatase score were useful in making a distinction between chronic neutrophilic leukaemia and a neutrophilic leukaemoid reaction. We established that all these changes occur in both conditions. Toxic granulation and Döhle bodies are more consistently present in leukaemoid reactions but also occur quite frequently in chronic neutrophilic leukaemia. The neutrophil alkaline phosphatase score is increased in both conditions and is of no value in making a distinction.

**Introduction**

As defined in the 2008 WHO classification (Bain, *et al* 2008), chronic neutrophilic leukaemia (CNL)  is a Ph-negative myeloproliferative neoplasm (MPN) characterised by a white cell count (WBC) of at least $25 \times 10^9$/l with segmented neutrophils and band forms comprising more than 80% of leucocytes, circulating blast cells less than 1%, immature granulocytes (promyelocytes, myelocytes and metamyelocytes) less than 10% and monocytes less than $1.0 \times 10^9$/l. There is no evidence of another MPN or a myelodysplastic syndrome (MDS), no dysplasia in any lineage and no evidence of a myelodysplastic/myeloproliferative neoplasm (MDS/MPN). There should be no identifiable cause of physiological neutrophilia or, if such is present, there should be evidence of clonality. From the early 1900s onwards, more than 200 cases of CNL have been described but many of these would not meet current diagnostic criteria. The first known case meeting current criteria is that described by Tuohy in 1920 as 'A case of splenomegaly with polymorphonuclear neutrophil hyperleukocytosis' (Tuohy 1920). However four other early cases had atypical features and appear more likely to have been primary myelofibrosis (Emile-Weil and Sée 1932, Hirschfeld 1904, Rathery 1902).

It is important to distinguish CNL from the neutrophilic leukaemoid reaction that can occur with multiple myeloma (plasma cell myeloma) and monoclonal gammopathy of undetermined significance (MGUS), which is attributable to cytokine release by neoplastic plasma cells. We were interested in reports of toxic granulation and Döhle

bodies in patients considered to have CNL and we have also observed these phenomena in neutrophilic leukaemoid reactions. Since toxic granulation is uncommon in myeloid neoplasms, this caused us to question whether some cases diagnosed as CNL might in fact have had a leukaemoid reaction to a plasma cell neoplasm. An increased neutrophil alkaline phosphatase (NAP) has similarly been described in CNL and in neutrophilic leukaemoid reactions. We therefore reviewed published cases of CNL to ascertain whether toxic granulation, Döhle bodies, other cytological abnormalities or an increased NAP were features of cases with a firmly established diagnosis of CNL. We similarly reviewed reported cases of plasma cell-associated neutrophilic leukaemoid reaction. We sought to relate any cytological abnormalities in neutrophils to the mutation in *CSFR3*, which is strongly associated with CNL (Maxson*, et al* 2013).

**Methods**

We identified and reviewed published cases of chronic neutrophilic leukaemia without an apparent coexisting plasma cell neoplasm. We similarly reviewed reports of patients with 'chronic neutrophilic leukaemia' or a neutrophilic leukaemoid reaction associated with multiple myeloma or monoclonal gammopathy or undetermined significance (MGUS). Our review included mainly cases published in English but also a small number of cases published in French, Italian or Spanish; we read all available abstracts of cases published in other languages (mainly Japanese and Korean). We excluded from the analysis, patients with features of polycythaemia vera, essential thrombocythaemia or primary myelofibrosis. We similarly excluded cases with monocytes of $1.0 \times 10^9$/l or more, with other evidence of MDS/MPN, with significant dysplasia, or in whom the 'CNL' represented evolution from MDS. In the cases with a confirmed diagnosis of CNL and in those with multiple myeloma or MGUS we reviewed written descriptions of neutrophil morphology and published photographs of blood films in order to assess the presence of toxic granulation, Döhle bodies or other cytological abnormalities. We also documented whether NAP was reduced, normal or elevated.

**Results**

At least 53 cases published as 'chronic neutrophilic leukaemia' did not meet current diagnostic criteria. We excluded from further consideration a total of eleven cases with features of polycythaemia vera (Billio*, et al* 2001, Castelli*, et al* 2015, Exton-Smith and Chazan 1957, Fujisawa*, et al* 1992, Harada*, et al* 1993, Higuchi*, et al* 1999, Iurlo*, et al* 1990, Lee*, et al* 2004, Lugassy and Farhi 1989, Shirakura*, et al* 1979, Tsurumi*, et al* 2002), nine cases with essential thrombocythaemia (Boggs and Kaplan 1986, Di Donato*, et al* 1986, Kunishima*, et al* 1989, Orazi*, et al* 1989, Zittoun*, et al* 1994) (case 2), (Noguchi*, et al* 2001, Ramya*, et al* 2014, Terré*, et al* 1999, Zhang*, et al* 2013) and two cases with primary myelofibrosis (Hirayama*, et al* 1994, Silberstein*, et al* 1974). We similarly excluded 15 cases with evidence of significant dysplasia or in whom the 'CNL' represented evolution from MDS (Cervantes*, et al* 1988, Cervantes*, et al* 1990, Mehrotra*, et al* 1985, Zoumbos*, et al* 1989) (four cases), (Dash*, et al* 1990, Zittoun*, et al* 1994) (case 3), (Carulli*, et al* 2010, Lee*, et al* 2001, Merlat*, et al* 2000, Ota*, et al* 2000, Pascucci*, et al* 1997, Takamatsu*, et al* 1996, Yamamoto*, et al* 2002) and also eight patients in whom there was evidence of MDS/MPN, such as monocytosis or significant numbers of

granulocyte precursors (Kaplan, *et al* 1992, Nakamine, *et al* 1988, Zittoun, *et al* 1994) (Case 1), (Katsuki, *et al* 2000, Pardanani, *et al* 2013 (cases 2 and 7), Piliotis, *et al* 2002, Quintero 2004) We did accept one case with a platelet count of $800 \times 10^9$/l as this count was three months after splenectomy (Orazi, *et al* 1989). We excluded one patient in whom the reported WBC was only $11.3 \times 10^9$/l (Bohm and Schaefer 2002), one with a WBC of $13.6 \times 10^9$/l (Zittoun, *et al* 1994), (case 1), two with counts of 15.5 and $16.2 \times 10^9$/l respectively (Saitoh and Shibata 1996) and three in whom the neutrophils were 65% (Yasui, *et al* 2003), 68% (Bohm and Schaefer 2002) and 74% (Bohm and Schaefer 2002) but we did include several patients in whom CNL appeared to be the most likely diagnosis but the reported WBC did not quite reach the $25 \times 10^9$/l or the neutrophils were not quite the >80% required by the WHO classification; this approach is justified by the variability of the WBC and percentage of neutrophils over time. A single patient was excluded as there was rearrangement of *PDGFRA* (Jain, *et al* 2013). After exclusion of a total of 53 cases, there remained for review a total of 146 patients with CNL without an apparent plasma cell neoplasm (Table 1). Fifteen patients had cytologically normal neutrophils. Toxic granulation was observed in 22 patients; in 11 of these cases Döhle bodies were also present, in one with accompanying vacuolation, and in two there was also neutrophil hypersegmentation. In one recent report of nine patients, one patient had documented toxic granulation and Döhle bodies and it was stated that these were common morphological features in patients with a *CSFR3* mutation (Maxson, *et al* 2013). Ring neutrophils were noted in four patients in a single publication (Kanoh, *et al* 1986) and one patient had neutrophil hypersegmentation without other abnormal features (Sugino, *et al* 2009). In nine cases there was some reference to morphology but insufficient for a judgement to be made as to what changes were actually present. In 95 patients there was neither a description of the morphological features of neutrophils nor an interpretable image.

The NAP was elevated in 82 cases of CNL, normal in six and low in two. In 56 cases this information was not available.

Because of the paucity of information, it was difficult to relate cytology and NAP to specific genetic abnormalities associated with CNL. Of the eight patients with a *CSF3R* mutation reported by Maxson et al. (Maxson, *et al* 2013), five of whom also has a *SETBP1* mutation (Gotlib, *et al* 2013), one was reported as having toxic granulation and Döhle bodies and it was stated that these were common morphological features in patients with a *CSFR3* mutation; NAP was not reported. Information on cytology and NAP was not available for the 10 patients reported by Pardanani *et al*., who met the WHO criteria for CNL and who has a *CSF3R* mutation, in two cases accompanied by a *SETBP1* mutation (Pardanani, *et al* 2013). Information was similarly not available for a total of 10 further patients with a *CSFR3* mutation, often accompanied by a *SETBP1* or *ASXL1* mutation (Cui, *et al* 2014, Lasho, *et al* 2014, Menezes, *et al* 2013). Of 14 reported cases with *JAK2* V617F, toxic granulation was present in two, in one case associated with Döhle bodies, one case showed hypersegmented neutrophils and five were cytologically normal; there was no useful information available in six cases (Gajendra, *et al* 2014, Imashuku, *et al* 2012, Kako, *et al* 2007, Lea, *et al* 2006, Maxson, *et al* 2013, Mc Lornan, *et al* 2005, Ortiz-Cruz, *et al* 2012, Steensma, *et al* 2005, Sugino, *et al* 2009, Thiele 2009,

Uemura, *et al* 2009, Wang, *et al* 2014). Six of the 14 patients had a high NAP and in eight information on NAP was not available.

There were a total of 49 patients with 'CNL' or neutrophilic leukaemoid reaction associated with multiple myeloma or MGUS (Table 2). Since MGUS is not rare in the age range in which CNL usually occurs, we cannot exclude that some patients did actually have both CNL and a plasma cell neoplasm. This is so for a patient who developed *CSF3R*-mutated CNL two years after detection of MGUS (Blombery, *et al* 2014) and for a patient in whom there was both smouldering myeloma and a homozygous *JAK2* V617F mutation (Nedeljkovic, *et al* 2014). The co-existence of two unrelated conditions also seems likely in a patient in whom the neutrophilia diminished as the myeloma became manifest (Rovira, *et al* 1990). Evolution of 'CNL' into acute myeloid leukaemia (AML) might be taken as evidence of the neoplastic nature of the apparent CNL; however in three patients in whom this occurred there had been prior treatment with leukaemogenic drugs such as busulphan and melphalan (Tursz, *et al* 1974) (patient 4), (Dincol, *et al* 2002, Lewis, *et al* 1986) so these cases were not excluded from the analysis. Case 4 reported by Zoumbos et al (Zoumbos, *et al* 1989) is of interest as this patient presented with 'CNL' and subsequently developed both kappa light chain myeloma and acute myeloid leukaemia; however the patient had trilineage myelodysplasia and so, with current diagnostic criteria, the initial presentation was as MDS/MPN rather than CNL . Having excluded the three patients in whom coexistence of two unrelated conditions was definite or likely, there remained 46 patients for analysis. Morphology of the neutrophils was described or illustrated in 28 cases and was not available in 18. Toxic granulation (Figure 1) was common, being reported in 25 of 27 described cases; it was often associated with the presence of Döhle bodies (11 cases), vacuoles (1 patient) or both (1 patient). A further patient had Döhle bodies without toxic granulation. Neutrophils appeared normal in two patients. NAP was available in 31 patients; it was increased in 28, normal in two and very low in one.

The associated plasma cell neoplasm was multiple myeloma in 27 cases, MGUS in 18 cases and plasmacytoma in one case. Kappa light chains were expressed in 15 patients, lambda in 22 and both light chain types in one patient; in eight patients this information was not available.

Comparison of data from the two groups of patients shows that toxic granulation and Döhle bodies are observed not infrequently in CNL but are more consistently associated with a neutrophilic leukaemoid reaction (Table 3). A high NAP is equally common in the two groups of disorders (Table 4).

**Discussion**

The lack of any specific cytogenetic abnormality has complicated the accurate diagnosis of CNL; until recently, information on molecular genetic abnormalities was also sparse so that there was often no evidence of clonality in cases in which this diagnosis was made. This situation has altered with the recent description of a strong association between a mutation in *CSFR3*, encoding the receptor for granulocyte colony-stimulating factor (G-CSF) (Maxson, *et al* 2013) and a diagnosis of CNL and the subsequent reporting of a co-existing mutation of *SETBP1* or *ASXL1* in a significant proportion of patients (Cui, *et al* 2014, Lasho, *et al* 2014, Menezes, *et al* 2013). Maxon *et al*. detected a *CSFR3* mutation

in eight of nine patients with CNL and in eight of 20 patients with a diagnosis of atypical chronic myeloid leukaemia (aCML) (Maxson, *et al* 2013). In a subsequent series of patients reported by Pardanani *et al*. in whom the diagnosis was reviewed before the molecular results were known, *CSFR3* mutation was found in all 12 patients with confirmed CNL (without MGUS); this series included three patients in whom the diagnosis of CNL was accepted but the WHO criteria were not quite met (one with 11% immature granulocytes, one with 10% monocytes and one with 78% rather than >80% neutrophils) (Pardanani, *et al* 2013). Pardanani *et al*. found no *CSFR3* mutation in 9 patients designated aCML in whom exons 14–17 were screened and mutation was similarly absent in 94 patients with chronic myelomonocytic leukaemia (CMML) and in 76 with primary myelofibrosis in whom only exon 14 was analysed (Pardanani, *et al* 2013). In this series, an additional mutation in *SETBP1* was found in four of 12 cases of *CSFR3*-mutated CNL (Pardanani, *et al* 2013). *CSFR3* mutation was absent in 5 patients with a plasma-cell neoplasm who were considered to meet the WHO criteria for CNL (Pardanani, *et al* 2013). In a third series of patients with CNL, a *CSFR3* mutation was found in six of 14 patients with CNL, two of 58 with aCML and two of 146 with chronic myelomonocytic leukaemia (Meggendorfer, *et al* 2014). Other mutations found in patients with CNL in this third series were *ASXL1* (8/14 cases), *TET2* (4/4 cases), *SRSF2* (3/14) and *SETBP1* (2/14 cases), with only *SETBP1* mutation coexisting with *CSFR3* mutation; only mutation of *CSFR3* was significantly more common in CNL than in aCML and CMML. In addition to these recently characterised molecular genetic abnormalities, at least 14 cases of CNL with a *JAK2* V617F mutation have been reported (Gajendra, *et al* 2014, Imashuku, *et al* 2012, Kako, *et al* 2007, Lea, *et al* 2006, Lee, *et al* 2012, Mc Lornan, *et al* 2005, Ortiz-Cruz, *et al* 2012, Pardanani, *et al* 2013, Steensma, *et al* 2005, Sugino, *et al* 2009, Uemura, *et al* 2009) Gajendra 2014 (3 cases)). In addition, *JAK2* V617F was found in a further patient with a clinical diagnosis of CNL but with a WBC of only $16.7 \times 10^9$/l (85% neutrophils) (Pardanani, *et al* 2013).

Our assessment of the significance of toxic granulation and Döhle bodies was made difficult by the very inexact diagnostic criteria that have been applied since the disease was first described in 1920. We can only reiterate the comment of Reilly (Reilly 2002) that "The literature … is frequently confusing and often incomplete". In addition, many reports make no mention of neutrophil cytology so that the number of cases that could be assessed was considerably fewer than the total reported. Despite this, we have demonstrated that toxic granulation can occur in both CNL and in neutrophilic leukaemoid reactions but is much more consistently present in the latter. We were unable make an adequate assessment of neutrophil cytology in relation to *CSFR3* or other mutations as recent papers focusing on molecular abnormalities have included few morphological details. We observed an increased NAP in both CNL and plasma cell-associated neutrophilia with a similar frequency being observed in the two groups of patients.

Truncating mutations of *CSF3R* can lead to both constitutive overexpression of the receptor and also to ligand hypersensitivity while proximal membrane mutations render cells ligand independent (Maxson, *et al* 2013). We postulate that truncating and possibly

other mutations of *CSF3R* can lead to toxic granulation and Döhle bodies in CNL whereas in neutrophilic leukaemoid reactions associated with plasma cell neoplasms similar cytological changes result from the synthesis of G-CSF by neoplastic plasma cells, which has been repeatedly demonstrated (Kohmura*, et al* 2004, Kusaba*, et al* 2004, Nagai*, et al* 1996, Rodríguez-Medina*, et al* 2013, Saitoh and Shibata 1996, Sebasky*, et al* 2008, Usuda*, et al* 1997).

We have confirmed the already reported preferential association of a neutrophilic leukaemoid reaction with lambda-expressing neoplastic plasma cells (Reilly 2002, Standen*, et al* 1990). Nevertheless only 59% of strictly defined cases were lambda-associated.

The discovery of the *CSFR3* and other mutations in CNL is likely to make a major contribution to the diagnosis of CNL and it seems possible that this will lead to a redefinition of the WHO diagnostic criteria. Consideration of the extent to which the WHO criteria might be altered if a *CSFR3* or other relevant mutation is demonstrated awaits the availability of further data. It seems prudent to require evidence of clonality of myeloid cells before making a diagnosis of CNL in a patient with MGUS or multiple myeloma since the majority of cases in which this diagnosis is suspected represent a leukaemoid reaction. Conversely, demonstration of polyclonal neutrophils (Standen*, et al* 1993) or increased plasma G-CSF provides strong supporting evidence for a diagnosis of a leukaemoid reaction. The presence of toxic granulation and Döhle bodies is more likely in a leukaemoid reaction than in CNL but the NAP does not aid in the distinction and is now of little diagnostic value.

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The two authors together performed  the research, carried out the analysis and wrote the paper.

**Legend for figure**
Peripheral blood film from an unpublished case of neutrophilic leukaemoid reaction associated with multiple myeloma showing neutrophilia, toxic granulation, increased background staining and rouleaux formation.

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Table 1
Summary of cases of chronic neutrophilic leukaemia in which cytological features of
neutrophils were described or illustrated.

| Age and gender | WBC (× $10^9$/l), neutrophils | Description of neutrophils | NAP | References |
|---|---|---|---|---|
| 58/F | 65, 99% | Normal granules | NA | (Tuohy 1920) |
| 72/M | 60, 96% | Not described | High | (Tanzer, *et al* 1964) |
| 76/F | 15–45, >85% | 'Shift to the left' | High | (Gingold, *et al* 1964) |
| 66/F | 50, 95% | Not described | High | (Jackson and Clark 1965) |
| 58/M | 69.4, 98% | Döhle bodies present over 2½ years; no TG apparent in photograph | High | (Rubin 1966) |
| 74/M | 27, 80% | Not described | High | (Shindo, *et al* 1977) |
| 60/M (case 1) | 89, 78%; later 188, 85% | Döhle bodies and prominent TG | High | (You and Weisbrot 1979) |
| 81/M (case 2) | 39.7, 94% | Döhle bodies and prominent TG | High | (You and Weisbrot 1979) |
| 74/M | 166.5, 91% | Döhle bodies | High | (Aoki, *et al* 1979)* |
| 49/M | 132, 96% | Not described | High | (Bareford and Jacobs 1980) |
| 49/M | NA | TG in photograph | High | (Yam 1982) |
| 67/M | 71.5, 96% | Normal | High | (Dotten, *et al* 1982) |
| 50/M | 25.2, 76% | Normal | High | (Feremans, *et al* 1983) |
| 66/M | 66, 87% | Not described | High | (Sponza, *et al* 1985) |
| 75/F (case 1) | NA | 2% ring-shaped nuclei | High | (Kanoh, *et al* 1986) |
| 53/M (case 2) | NA | 3.5% ring-shaped nuclei | High | (Kanoh, *et al* 1986) |
| 70/M (case 3) | NA | 3% ring-shaped nuclei | High | (Kanoh, *et al* 1986) |
| 26/F (case 4) | NA | 10% ring-shaped nuclei | High | (Kanoh, *et al* 1986) |
| 72/F | 129, 81% | Not described | High | (Hossfeld, *et al* |

| (case 1) | | | | 1987) |
|---|---|---|---|---|
| 71/F (case 2) | 101, 89% | Not described | Normal then high | (Hossfeld, *et al* 1987) |
| 56/F | 33.7, 79% | Not described in abstract | High | (Nakase, *et al* 1987)* |
| 63/M | 30.4–51, 75–85% | TG | High | (Lim, *et al* 1987)† |
| 40/F | 10–36, 91% | Not described | High | (Tang, *et al* 1987) |
| 45/F | 35, 86% | Not described | High | (Sundar, *et al* 1988) |
| 71/M | 49.6, NA | Not described in abstract | High | (Tohyama, *et al* 1988) |
| 77/F | 45.9, 92% | Not described | High | (Lorente, *et al* 1988) |
| 71/M | 51.6, 94% | Döhle bodies and prominent TG | High | (Orazi, *et al* 1989) |
| 67/M | 105, 88% | Not described in abstract | High | (Okada, *et al* 1989)* |
| 81/F | 31.9, 96% | TG and Döhle bodies | High | (Oogushi, *et al* 1989) |
| 78/M | NA | 'Mature neutrophils' | High | (Wang, *et al* 1990)* |
| 77/M | 62–73, 89–95% | 'A few toxic granulations' | High | (Ho and Wang 1991) |
| 79/F | 40.1, 83% | Not described | High | (Churdchu, *et al* 1991) |
| 48/M | 38, 87% | Not described | High | (Storek 1992) |
| 65/M | 37.5, 84% | TG, Döhle bodies | High | (Ohtsuki, *et al* 1992) |
| 65/F (case 1) | 93, 89% | Not described | High | (Kaplan, *et al* 1992) |
| 61/M (case 2) | 110, 96% | Not described | High | (Kaplan, *et al* 1992) |
| 65/M (case 3) | 48.4, 83% | Not described | High | (Kaplan, *et al* 1992) |
| 80/F (case 6) | 73, 81% | Not described | High | (Kaplan, *et al* 1992) |
| 76/M | 146, 83% | TG, vacuoles and Döhle bodies | High | (Jeon, *et al* 1992)* |
| 68/F (case 1) | 36.8, 86% | Not described | NA | (Meyer, *et al* 1993) |
| 70/F (case 2) | 31.9, 94% | Not described | High | (Meyer, *et al* 1993) |

| 60/F | 100, 98.5% | 'No dysplasia' | High | (Kwong and Cheng 1993) |
|---|---|---|---|---|
| 74/M | 20–40, 80% | Not described | High | (Castanet, *et al* 1993) |
| 70/M | 41, 82% | Mainly normal, no TG or Döhle bodies | High | (Takemori, *et al* 1994) |
| 65/M (case 1) | 19.7–31.4, 92% | Not described | High | (Zittoun, *et al* 1994) |
| 15/F (case 1) | 40.2, 88% | Not described | High | (Hasle, *et al* 1996) |
| 25/M (case 2) | 45.7, 89% | Not described | NA | (Hasle, *et al* 1996) |
| 75/M | 84.6, 92% | TG | High | (Cho, *et al* 1996)‡ |
| NA (case 3) | 50.2, 90% | Not described | High | (Saitoh and Shibata 1996) |
| NA (case 4) | 46.5, 91% | Not described | High | (Saitoh and Shibata 1996) |
| NA (case 5) | 48.8, 91% | Not described | High | (Saitoh and Shibata 1996) |
| 67/F | 36.7, 81% | Photograph shows possible TG | High | (Matano, *et al* 1997) |
| 68/M | 156, 86% | Not described | High | (Perez-Simon, *et al* 1997) |
| 63/M | 84, 92% | 'Left shift' | High | (Yanagisawa, *et al* 1998), (Kojima, *et al* 1999) |
| 44/M | 12–24.7, 84% | Not described | High | (Kojima, *et al* 1999) |
| 76/F | 49.7, 97% | Normal | High | (Frank, *et al* 2000) |
| 74/F | 85 | Not described but appear normal in photograph | Normal | (Willard, *et al* 2001) |
| 68/M | 58, 78% | TG and Döhle bodies | NA | (Umashankar, *et al* 2001) |
| 56/M | 40.8, 90% | Not described | NA | (Hara, *et al* 2001) |
| 65/F (case 1) | 116, 94% | Not described | High | (Kobayashi, *et al* 2002) |
| 61/M (case 2) | 74.5, 80.8% | Not described | High | (Kobayashi, *et al* 2002) |
| 68/M (case 3) | 34.7, 86.5 | Not described | High | (Kobayashi, *et al* 2002) |

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| 40/F (case 1) | 22.6, 84% | Not described | High | (Bohm and Schaefer 2002) |
| 69/M (case 4) | 49.2, 88% | Not described | Very low | (Bohm and Schaefer 2002) |
| 77/F (case 5) | 89, 95% | Not described | Normal | (Bohm and Schaefer 2002) |
| 64/M (case 6) | 41.7, 84% | Not described | Normal | (Bohm and Schaefer 2002) |
| 81/F (case 8) | 35, 95% | Not described | High | (Bohm and Schaefer 2002) |
| 37/F (case 9) | 36.3, 92% | Not described | High | (Bohm and Schaefer 2002) |
| 72/F (case 10) | 38, 90% | Not described | Low | (Bohm and Schaefer 2002) |
| 64/M (case 11) | 109, 87% | Not described | High | (Bohm and Schaefer 2002) |
| 52/F (case 12) | 30, 82% | Not described | High | (Bohm and Schaefer 2002) |
| 72/M (case 13) | 22.8, 82% | Not described | Normal | (Bohm and Schaefer 2002) |
| 63/F (case 14) | 24.6, 78% | Not described | Normal | (Bohm and Schaefer 2002) |
| 42/F | NA | Not described | NA | (Reilly 2002) |
| 58/F | 36.5, 92% | Not described | NA | (Hasegawa, *et al* 2003) |
| 54/F | 36.6, 89.7% | 'Mild dysplastic features' (not specified) | High | (Yoshida, *et al* 2004) |
| 48/M | 45 | TG | High | (Choi, *et al* 2004) |
| 54/M | 32, 85% | Normal | High | (Krishnan, *et al* 2004) |
| 80/M | 28, 90% | Some TG | High | (Sai, *et al* 2004) |
| 66/F (case 1) | 71, 94% | Not described | High | (Elliott, *et al* 2001, Elliott, *et al* 2005) |
| 66/F (case 2) | 125.7, 88% | Not described | High | (Elliott, *et al* 2001, Elliott, *et al* 2005) |
| 55/M (case 3) | 103.3, 85% | Not described | High | (Elliott, *et al* 2001, Elliott, *et al* 2005) |
| 74/M (case 4) | 50, 94% | Not described | NA | (Elliott, *et al* 2001, Elliott, *et al* 2005) |

| 54/M (case 5) | 36.4, 89.5% | Not described | High | (Elliott, *et al* 2001, Elliott, *et al* 2005) |
|---|---|---|---|---|
| 86/M (case 6) | 64.7, 89% | Not described | NA | (Elliott, *et al* 2001, Elliott, *et al* 2005) |
| 71/M (case 7) | 26.9, 81% | Not described | NA | (Elliott, *et al* 2005) |
| 47/M (case 8) | 22.6, 87% | Not described | NA | (Elliott, *et al* 2005) |
| 85/M (case 9) | 41.5, 83% | Not described | NA | (Elliott, *et al* 2005) |
| 77/M (case 10) | 47.1, 82% | Not described | NA | (Elliott, *et al* 2005) |
| 78/M (case 11) | 29.4, 76% | Not described | NA | (Elliott, *et al* 2005) |
| 72/M (case 12) | 58.7, 82% | Not described | NA | (Elliott, *et al* 2005) |
| 61/M | 54, 88% | 'Segmented neutrophils' | NA | (Mc Lornan, *et al* 2005) |
| NA | NA | Not described | NA | (Steensma, *et al* 2005) |
| 68/M | 55.3, 88.5% | Not described | NA | (Izumi, *et al* 2005) |
| 56/F | 39.1, 86% | 'Mature neutrophilia' | NA | (Lea, *et al* 2006) |
| 44/M | 33.6, 91% | Not described | High | (Bhave, *et al* 2006) |
| 46/M | 23.8, 89% | Not described but photograph of BM does not show TG | NA | (Kako, *et al* 2007) |
| 74/M | 79.3, 89% | Not described but photograph of BM does not show TG | High | (Gan, *et al* 2007) |
| 83/F | 29, 92.8% | Not described | Normal | (Shigekiyo, *et al* 2008) |
| 81/M | 30.7, 75% | Not described | NA | (Neureiter, *et al* 2008) |
| 68/F | 42, 88% | TG, photograph shows Döhle bodies | High | (Amato, *et al* 2008) |
| 23/M | 19.8, 85% | TG and Döhle bodies | High | (Goto, *et al* 2009) |
| 70/F | 37.4, 88% | Hypersegmented neutrophils | High | (Sugino, *et al* 2009) |
| 86/F | 32.4, 85% | 'No dysplastic features' | High | (Uemura, *et al* |

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| | | | | 2009) |
| 70/M | 49, NA | TG | NA | (Thiele 2009) |
| 59/M | 137, 96% | TG, some hypersegmentation | NA | (Ziai, *et al* 2010) |
| 64/M | 124, 102% (sic) | Photograph does not show TG | NA | (Ortiz-Cruz, *et al* 2012) |
| 80/M | 31.9, 91.9% | Not described | High | (Imashuku, *et al* 2012) |
| 61/M | 52.1, 79% | Photograph does not show TG | High | (Chen, *et al* 2013) |
| 73/F (case 10) | 178.6, 96% | TG and Döhle bodies | NA | (Maxson, *et al* 2013) |
| Eight further cases | | Not described but TG and Döhle bodies stated to be 'common morphologic features among CNL … patients carrying *CSF3R* mutations' | NA × 8 | (Maxson, *et al* 2013) |
| Ten cases | | Not described | NA × 10 | (Pardanani, *et al* 2013) |
| 66/M | 66. 91.5 | No dysplasia | NA | (Menezes, *et al* 2013) |
| 39/F | 124.8, NA | Not described | NA | (Taylor, *et al* 2013) |
| 66/F | 180, NA | Not described | NA | (Lasho, *et al* 2014) |
| 64/M | 34, >90% | TG, hypersegmentation | High | (Ranjan, *et al* 2014) |
| 53/F (case 1) | 34, 93% | Normal | High | (Gajendra, *et al* 2014) |
| 59/M (case 2) | 29, 88% | Normal | High | (Gajendra, *et al* 2014) |
| 61/M | 42, 88% | Normal | High | (Gajendra, *et al* 2014) |
| 45/M | 70, 90% | TG | High | (Rane, *et al* 2014) |
| Eight cases | | Not described × 8 | NA × 8 | (Cui, *et al* 2014) |
| 41/F | 61.7, 85% | TG and Döhle bodies | NA | (Wang, *et al* 2014) |
| 33/M | 71.8. 81% | No TG | NA | Kaur 2015 |

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Abbreviations: BM, bone marrow; CNL, chronic neutrophilic leukaemia; F, female; M, male; NA, not available; NAP, neutrophil alkaline phosphatase; TG, toxic granules; WBC, white blood cell count

\* Abstract only read, article in Japanese
† Abstract and tables only read, article in Korean
‡ Article in Korean, only part available in English
§ Abstract only read, article in Korean

Table 2

Chronic neutrophilic leukaemia or neutrophilic leukaemoid reaction associated with a plasma cell neoplasm

| Age and gender | WBC (× $10^9$/l), neutrophils | Description of neutrophils | NAP | Nature of plasma cell neoplasm | References |
|---|---|---|---|---|---|
| 74/M (Patient 3) | 46.6, 85% neutrophils (monocytes $2.7 \times 10^9$/l, 6%) | TG and Döhle bodies | High | IgA lambda MM | (Tursz, *et al* 1974) |
| 60/F (Patient 4) | 28, 95% | TG | NA | IgG lambda MM* | Tursz 1974 |
| 68/F | 30, 90% neutrophils | TG | High | IgG lambda MM | (Carcassonne, *et al* 1977) |
| 70/M | 19, 88% | TG and Pelger-Huët anomaly | High | IgA kappa MM | (Vorobiof, *et al* 1978) |
| 57/F | 40 | Not described | High | IgG kappa MM | Nakahara 1978, cited by Watanabe and di Guglielmo |
| 60/M | 35.9, 90% | Not described | High | IgA lambda MGUS | (Naparstek, *et al* 1980) |
| 64/F | 35, 80%; 5% granulocyte precursors | Normal | Normal | IgG lambda MM 15 years after 'CNL' | (Franchi, *et al* 1984) |
| 71/M | 77.6, 89% | TG and Döhle bodies | High | IgG lambda and IgA kappa MGUS | (Watanabe, *et al* 1984) |
| 65/F | 57, 87% | TG | High | IgG lambda MGUS | (Mehrotra, *et al* 1985) |
| 67/F (case 1) | 25.3, 91% | TG and Döhle bodies | High | IgA lambda MGUS, later MM | (Lewis, *et al* 1986) |
| 72/F (case 2) | 36.3, 91% | Not described | High | Ig A lambda MM† | (Lewis, *et al* 1986) |
| 68/M | 35, 94% | TG | High | IgA kappa | (Di Guglielmo, *et* |

| | | | | MGUS | *al* 1986) |
|---|---|---|---|---|---|
| 57/M | 55.4, 90% | Not described | Very low | Kappa MM five years after presentation | (Zoumbos, *et al* 1987) |
| 31/F | 23.9, 82% | Not described | High | Kappa Bence-Jones MM 7 years after presentation with 'CNL', WBC then fell[‡] | (Rovira, *et al* 1990) |
| NA | NA | TG and Döhle bodies | NA in abstract | IgG lambda MM | (Dieguez, *et al* 1992) |
| 76/M | 22.3, 85% | Not described | High | IgG kappa MGUS | (Masini, *et al* 1992) |
| 76/F (case 1) | 72.3, 91% | TG and Döhle bodies | High | IgG lambda MM | (Standen, *et al* 1990) |
| 65/F (case 2) | 32, 86% | TG and occasional Döhle body | High | Plasmacytoma with an IgG lambda paraprotein, later MM | (Standen, *et al* 1990) |
| 73/F | 25, 83% | Numerous Döhle bodies | High | IgA lambda MM | (Troussard, *et al* 1992) |
| 58/F | 23, 80% | Not described | High | IgG kappa MM | (Troussard, *et al* 1992) |
| 61/F | 66, 90% | TG, vacuolation, Döhle bodies | High | IgA lambda MGUS | (Florensa, *et al* 1993) |
| 60/F | 62.4, 85% | TG and Döhle bodies | High | Kappa Bence–Jones MM | (Cehreli, *et al* 1994) |
| 57/F | 33.4, 95% | TG (fibrillar inclusions on EM) | High | IgA lambda MM | (Mori, *et al* 1995) |
| 30/M | 42.2, 91% | TG | High | IgG kappa MGUS | (Ito, *et al* 1996) |
| 73/M | 28.08, 85% | Not described | High | IgG kappa MGUS | (Nagai, *et al* 1996) |
| 56/M | 99, 98% | Not described | High | IgA lambda MM | (Usuda, *et al* 1997) |
| 68/F | 50.9, 94% | TG and vacuoles | High | IgG lambda MM | (Kim, *et al* 1998) |
| 71/M | 38, 86% | TG and Döhle | High | IgG kappa | (DinÇol, *et al* |

| | | | | | |
|---|---|---|---|---|---|
| | | bodies | | MM[§] | 2002) |
| 68/M | 29.9, 82% | TG | High | Lambda Bence–Jones MM | (Kusaba, *et al* 2004) |
| 94/M | 31.3, 90.5% | No TG | Normal | IgG kappa MM | (Kohmura, *et al* 2004) |
| 74/M | 25.6, 71% | TG | High | Lambda Bence–Jones MM | (Fukuno, *et al* 2006) |
| 64/F | 93, 93% | TG | NA | IgG kappa MM | (Kim, *et al* 2007) |
| 40/F | 21, 76% | TG | High | IgM lambda MM | (Gnerre, *et al* 2007) |
| 56/M | 29, NA | TG and Döhle bodies | NA | IgG kappa MM | (Sebasky, *et al* 2008) |
| 66/F | 40–60, NA | Occasional TG | NA | IgA lambda MM (13% plasma cells) | (Thiele 2009) |
| 60/F | 44.11, 79% | Not described | High | IgA kappa MGUS | (Hartley, *et al* 2010) |
| 64/F | 25.4, 70% | Not described | High | IgA MGUS | (Cabrera Aguilar 2012) |
| 77/F | 45, 90% | Not described | High | IgA kappa MM | (Quiroz , *et al* 2010, Rodríguez-Medina, *et al* 2013) |
| 64/M | 28.7, 90% | Not described | NA | MGUS | (Pardanani, *et al* 2013) |
| 71/F | 48.4, 82% | Not described | NA | MGUS | (Pardanani, *et al* 2013) |
| 52/M | 27.8, 90% | Not described | NA | MGUS | (Pardanani, *et al* 2013) |
| 68/F | 138, 95% | Not described | NA | MGUS | (Pardanani, *et al* 2013) |
| 83/M | 114.3, 84% | Not described | NA | MGUS | (Pardanani, *et al* 2013) |
| 57/F | 114, 92% | TG | NA | IgG kappa MGUS with a normal blood count 2 years prior to developing CNL with *CSF3R* mutation[‡] | (Blombery, *et al* 2014) |
| 81/M | 26.8, NA | No TG or dysplasia | NA | IgG kappa smouldering MM, homozygous | (Nedeljkovic, *et al* 2014) |

| | | | | *JAK2* V617F[‡] | |
|---|---|---|---|---|---|
| 63/F | 65.5, 91% | TG and Döhle bodies | NA | Lambda Bence-Jones MM | (Taiwo, *et al* 2014) |
| 46/M (Case 9) | 65.3, 93% | Not described in English | NA in English | MGUS | (Cui, *et al* 2014) |
| 52/F (Case 10) | 26.53, 75% | Not described in English | NA in English | MGUS | (Cui, *et al* 2014) |
| 52/M | 22.5, 84%[¶] | TG and Döhle bodies | NA | IgG lambda MM | (Milojkovic, *et al* 2015) |

Abbreviations: CNL, chronic neutrophilic leukaemia; EM, electron microscopy; F, female; Ig, immunoglobulin; M, male; MGUS, monoclonal gammopathy of undetermined significance; NA, not available; MM, multiple myeloma.

\* Three years later developed acute myeloid leukaemia but had received cyclophosphamide and melphalan

[†] 'Blastic transformation' but patient had received melphalan and busulphan over the previous four years

[‡] Excluded from analysis as interpreted as two independent neoplasms

[§] 'Blastic transformation'1.5 years after presentation having had 6 cycles of melphalan

[¶] On hydroxycarbamide

Table 3

Comparison of cytological features in chronic neutrophilic leukaemia and neutrophilic leukaemoid reaction in patients for whom data were available

|  | Chronic neutrophilic leukaemia (n = 51) | Leukaemoid reaction (n = 28) |
|---|---|---|
| Toxic granulation and Döhle bodies | 11 | 11 |
| Toxic granulation without Döhle bodies | 11 | 14 |
| Döhle bodies without toxic granulation | 0 | 1 |
| Other or not clearly specified | 14 | 0 |
| Cytologically normal | 15 | 2 |

Table 4
Comparison of neutrophil alkaline phosphatase in chronic neutrophilic leukaemia and
neutrophilic leukaemoid reaction in patients for whom data were available

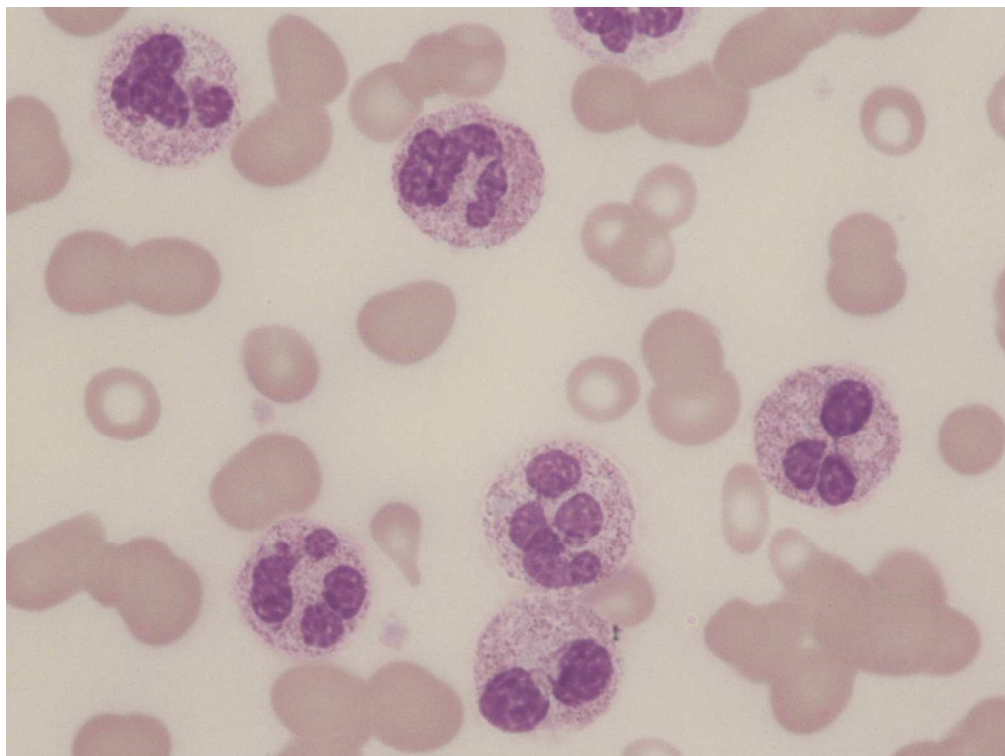|  | Chronic neutrophilic leukaemia (n= 90) | Leukaemoid reaction (n = 31) |
|---|---|---|
| High | 82 | 28 |
| Normal | 6 | 2 |
| Low | 2 | 1 |

Figure 1
67x50mm (300 x 300 DPI)